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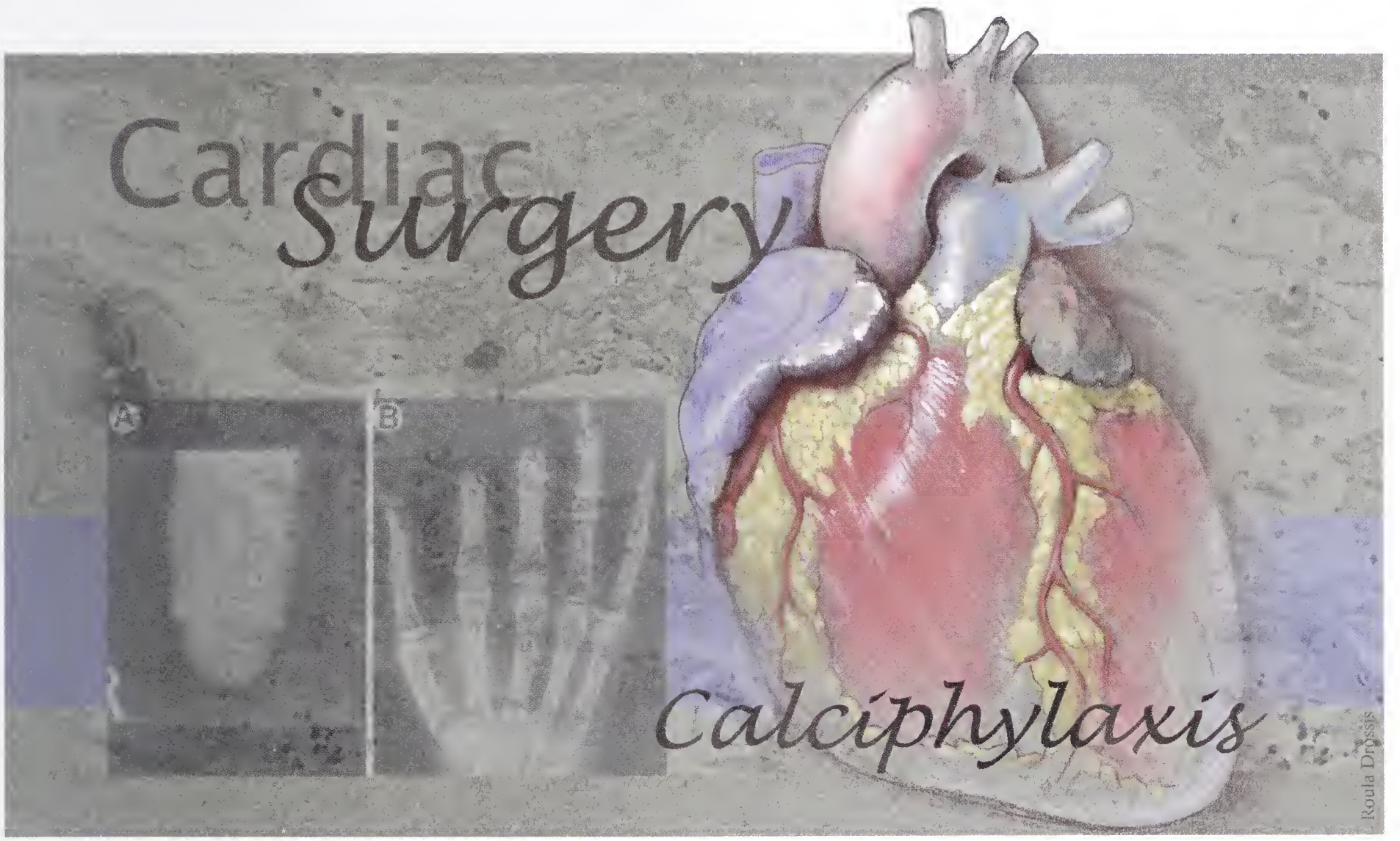

92 **Preface**

93 **Letter to the Editors**

94 **Coronary Artery Revascularization with Concomitant Bilateral Lung Volume Reduction Surgery without Cardiopulmonary Bypass**
Salvatore Privitera, Thomas R.J. Todd, and Robert J. Cusimano

98 **Calciphylaxis: A Review of Pathogenesis, Diagnosis and Treatment**
Dan Mozeg and Joanna Sasal

104 **Epileptic Seizures: Do They Cause Reproductive Dysfunction?**
Heather E. Edwards, Neil J. MacLusky, and W. McIntyre Burnham

112 **The Physiological Roles of Cadherin Mediated Cell Adhesion**
Anton Mak, Orest W. Blaschuk, and Gitte S. Jensen

118 NEWS AND VIEWS

157 MORNING REPORT

161 CLINICOPATHOLOGICAL CORRELATION

171 QUICK DIAGNOSIS

178 TECHNOLOGY REVIEWS

183 BOOK REVIEWS

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Table of Contents

92 **Preface**

93 **Letter to the Editors**

Case Report

94 Coronary Artery Revascularization with Concomitant Bilateral Lung Volume Reduction Surgery without Cardiopulmonary Bypass
Salvatore Privitera, Thomas R.J. Todd, and Robert J. Cusimano

Medicine

98 Calciphylaxis: A Review of Pathogenesis, Diagnosis and Treatment
Dan Mozeg and Joanna Sasal

Neurology

104 Epileptic Seizures: Do They Cause Reproductive Dysfunction?
Heather E. Edwards, Neil J. MacLusky, and W. McIntyre Burnham

Immunology

112 The Physiological Roles of Cadherin Mediated Cell Adhesion
Anton Mak, Orest W. Blaschuk, and Gitte S. Jensen

News and Views

118 In the Literature
Yvonne Chan and Stephen C. Juvet

122 In the Media
Edward C.W. Leung

125 Prolific Scientists Profiles: An Interview with Dr. Tak Wah Mak
Susan Quesnel

129 The Sixth Canadian Conference on International Health: Shifting Global Environments for Health and Development
Tara Kiran

131 Clinician-Scientists Accountable to Disparate Institutions: Hospital, University, and Industry
Martin C. Chang and Maria F. Muraca

133 Law and Ethics in Medicine: Informed Consent in the Clinical Setting
Fayez A. Quereshy and Hemant A. Shah

137 Law and Ethics in Medicine: HIV Testing in Pregnant Women: Ethical Considerations
Elizabeth Gold

139 Back to Basics Series: An Approach to the Chest X-Ray
Yvonne Chan, Stephen C. Juvet, and Stephen J. Herman

154 Evidence-Based Medicine: Practicing Evidence-Based Medicine
Evette Weil

Morning Report

157 Exploring a Pediatric Exanthem
Vance Tsai and Marcellina Mian

Clinicopathological Correlation

161 'Pseudomyxoma Peritonei: The Case of the Perplexed Primaries'
Eni J. Keszthelyi and Jennifer L. Shin

Quick Diagnosis

171 Internal Medicine Rounds
Christopher Tam and Lindsay Teskey

Technology Reviews

178 "Virtual" Radiology – Digital imaging takes on new importance at the University Health Network (UHN)
Carolyn J. Owen, Jean-Pierre Champagne, Anita Aggarwal, and Richard Bitar

181 Interactions: The IBIS Guide to Drug-Herb and Drug-Nutrient Interactions
Dan Perri

Book Reviews

183 Clinicians' Guide to Pain
Reviewed by Elizabeth Gold

185 Handbook of Clinical Nutrition
Reviewed by Andrew Brack

187 Sexual Medicine in Primary Care
Reviewed by Helen Dempster

189 Textbook of Medical Physiology and Review of Medical Physiology
Reviewed by Sharon Cushing and Angela Marrocco

191 History of Medicine: A Scandalously Short Introduction
Reviewed by Sacha Agrawa and Inbal Gafni

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Preface from the Editors

With the inauguration of the Editors' Award, the quality of recent submissions has been impressive. The diverse array of research interests from student authors continues to support the need for a student-run publication, such as the *UTMJ*, in which a sample of students' interests, both from a basic science and clinical perspective, can be surveyed. Thus, on behalf of the entire editorial staff, we are proud to offer the most recent samplings from the 77th volume.

In keeping with the refined vision of the *UTMJ*,[1] we present four feature articles that cover a broad range of topics from diverse fields of surgery, medicine, neurology, and immunology. Privitera *et al.* present an interesting surgical case of a patient who underwent lung volume reduction surgery with concomitant coronary artery bypass grafting, but without the use of cardiopulmonary bypass. According to the authors, this is the first time that such a case has been reported. Mozeg and Sasal overview a troublesome complication of end-stage renal disease: calciphylaxis. Edwards *et al.* review the literature and their own findings in order to gain an understanding of the mechanisms responsible for seizure-induced alterations in reproductive function. Lastly, Mak *et al.* address the physiological roles of cadherins in cell signalling, tumour responses, and immune responses.

In this issue, News and Views showcases articles that reflect both student opinion and commentary, and even a methodological approach to interpreting a chest x-ray! Morning Report explores the cause of a seemingly enigmatic exanthem on the pediatric wards and Clinicopathological Correlation thoroughly investigates the cause of a "perplexing" pelvic mass. Quick Diagnosis offers the internist an opportunity to test his/her skills.

With the recent conversion of the radiology departments at the University of Health Network to a "filmless" digital system for storing and retrieving imaging material, it is fitting that Technology Review examines the topic in detail. Finally, six books encompassing various aspects of medicine are concisely evaluated in Book Reviews.

In order to make accessing the *UTMJ* easier, we are continually updating our website with news and information. As well, back issues, instructions to authors, and patron forms can be found on our website (www.utmj.org). Comments and letters are always welcomed and can be directed to the Editors (e-mail: editors.utmj@utoronto.ca).

R.H.K. and P.K.S.
Editors-in-Chief

Reference

1. Kim RH and Stotland PK. (1999). A letter to our patrons. *UTMJ*. 77:4.

Letter to the Editors

Dear Editors,

Thank you for your correspondence announcing the Inaugural *UTMJ* Editor's Award.

The *UTMJ* has a proud history of encouraging budding health care researchers and has provided an excellent forum for the publication of their research articles and review papers. The Editors' Awards is a fitting way to celebrate 77 years of publication and is a testament to the many students who have kept the *Journal* alive and vibrant over the years.

The advancement of medical science has allowed us to enjoy a quality of health and life that was unimaginable in the last century. It is vitally important that our young scientists continue the Canadian tradition of excellence in medical research for today's research is tomorrow's health care.

The Canadian Medical Association is very pleased to support the efforts of the *UTMJ* to promote medical research, and the *UTMJ* Editors' Award.

Sincerely,

Hugh E. Scully, M.D., F.R.C.S.(C), F.A.C.S.
President, Canadian Medical Association

Coronary Artery Revascularization with Concomitant Bilateral Lung Volume Reduction Surgery without Cardiopulmonary Bypass

Salvatore Privitera, M.Sc. (0T2), Thomas R. J. Todd, M.D., F.R.C.S.(C),* and
Robert J. Cusimano B.Sc., M.Sc., M.D., F.R.C.S.(c), F.A.C.S.**

Abstract

Coronary artery revascularization with concomitant lung volume reduction surgery without cardiopulmonary bypass has never been reported as a combined operative procedure for concurrent cardiac and pulmonary disease. A patient is described who underwent bilateral lung volume reduction surgery with coronary artery bypass grafting without cardiopulmonary bypass, respectively, in the hope of reducing peri-operative morbidity. The procedure was performed through a median sternotomy in a single (combined) operative session.

Background

Patients with concomitant cardiac and pulmonary disease requiring surgical intervention are traditionally treated with two separate operations in a staged fashion depending on clinical priority. Occasionally, however, both are required concomitantly when each is separately indicated in order to reduce overall morbidity and/or mortality. Typically, such combined procedures involve coronary artery bypass grafting (CABG), using cardiopulmonary bypass (CPB), with pulmonary resection. However, concern exists regarding the adverse immunosuppressive and pulmonary effects of extracorporeal circulation. Diminished pulmonary function and increased capillary permeability, with the associated increase in lung water, may make combined procedures (using CPB) in those patients with poor pulmonary function especially dangerous. We describe a patient in whom bilateral lung volume reduction surgery (LVRS) was performed for severe emphysema with concurrent CABG without the use of CPB in a combined surgical procedure through a median sternotomy.

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Case Report

A 68-year-old wheelchair bound male with a previous anterior myocardial infarction and Alpha-1 anti-trypsin deficiency giving rise to severe bullous emphysema (FEV_1 of 0.4 L, pCO_2 of 50mmHg), further exacerbated by a 60-pack year smoking history, was deemed ineligible for lung transplant but was offered LVRS to improve pulmonary function. Preoperative work-up uncovered calcified coronary arteries and coronary disease with diffuse left anterior descending (LAD) and right coronary stenoses. The left ventricular size and function were normal. His functional capacity was limited by his respiratory status and he was asymptomatic from his coronary disease. LVRS without CABG was felt to carry too high a cardiac risk and his end stage emphysema precluded isolated CABG. Thus a combined CABG/LVRS was planned. Due to severely compromised pulmonary function and concerns related to CPB and the heart-lung machine, "off pump" techniques (CABG without CPB) were planned for his coronary bypass.

Double lumen endotracheal intubation and epidural analgesia were utilized in addition to standard techniques. A full median sternotomy was used. Bilateral lung volume reduction was carried out first, using multiple firings of the Autosuture GIA® stapler. Pericardial sleeves were employed to buttress the suture line. Due to the 10-15 cm distance between the sternum and the anterior surface of the heart, the internal thoracic artery was not utilized. A two-vessel

saphenous vein CABG was performed without CPB. The Medtronic Octopus II® stabilizer and Medtronic mister/blower devices and silastic snares, placed proximally on each vessel, were used for the anastamoses. The LAD and acute marginal branch of the right coronary artery (the only non-calcified portion of the right system) were bypassed. A complex atheromatous plaque was encountered when the aortotomy for the proximal anastomosis was performed (by partial aortic side-clamping), so a localized endarterectomy and saphenous vein patch were used. The 5,000 units of heparin used was reversed after construction of the bypasses. The patient was extubated in the operating room and returned to the intensive care unit (ICU) for further monitoring. He was discharged to the ward after 4 days but was readmitted to the ICU 8 days post-operatively when he developed bilateral basilar pneumonia and subsequently required prolonged ventilatory support. After developing another episode of pneumonia, the family elected not to pursue aggressive resuscitative measures and the patient passed away 6 months after his surgery.

Discussion and Conclusions

Several investigators[1-3] have described disadvantages and potential complications that can arise in combined CABG/lung resection, in particular during CPB. There is an increased risk of intrapulmonary hemorrhage on the heart-lung machine,[1] technical problems associated with anticoagulation and coagulopathy, and perioperative immunosuppression that might increase short-term infectious complications.[3,4] However, in patients undergoing combined procedures, CABG without CPB may be beneficial in reducing morbidity through decreased post-operative bleeding and transfusion requirements,[4,5] and the reduced incidence of pulmonary injury (fluid overload, activation of the inflammatory response, and endothelial cell injury)[6] and neurological complications.[7] A reduced heparin dose may also lead to a decreased risk of hemorrhage. In this case, only 5,000 units were administered as multiple firings of the GIA® stapler was deemed to increase the risk of intrapulmonary hemorrhage.

The operative mortality in patients with coexisting lung disease undergoing isolated CABG is significantly increased.[8] In addition, the perioperative risks of adverse cardiac events in patients undergoing stand-alone lung resection with significant coronary artery disease (CAD) is also substantially increased.[4,9] In these cases of combined operable co-morbidities, it therefore seems that a combined procedure would be called for. The early results of combined cardiac and pulmonary surgery were encouraging,[10,11] pointing to minimal increases in morbidity. One later study[12] found no increase in early or late morbidity or mortality while using the combined approach.

The concomitant occurrence of critical CAD and severe emphysema tends to be low. In one study, 20% of patients qualifying for LVRS demonstrated relevant, usually asymptomatic, CAD with normal left ventricular function.[9] Patients in this study with significant CAD (n=9) either had LVRS with no cardiac interventions (n=2) or pre-LVRS targeted percutaneous transluminal coronary angioplasty (PTCA) (n=2). Four patients were rejected from LVRS based entirely on significant two-vessel disease (n=3) or one-vessel disease (right coronary ostium) (n=1) not accessible to PTCA. Only one patient had pre-LVRS CABG using CPB whose outcome was uneventful.

In another study,[13] nine patients accepted for LVRS were also treated for their CAD. Patients either had LVRS with PTCA and/or stent (n=7) or LVRS and CABG with CPB (n=2) in a combined procedure. These CABG/LVRS patients both proceeded along an uneventful course, although there was no indication of when post-operative extubation occurred. Significant improvements in FEV_1 over the first six months were observed in all cases with values for the CAD patients equal to that of LVRS patients without CAD. The mean pre-operative FEV_1 for those patients was 0.73 +/– 0.05 L (as compared to 0.4 L in this case) indicating all their LVRS patients with CAD suffered from less severe pulmonary dysfunction. It is worth noting that the perioperative morbidity and mortality was similar to patients without CAD.

Median sternotomy was employed for surgical access in our patient. Although it may offer limited exposure for pulmonary surgery, in particular the posterior fields, it offers good exposure to both lung hila and has been the standard approach by some surgeons for routine pulmonary resection.[14] In this combined operative procedure a single incision through the midline permitted access to both lungs and the heart. In comparison to posterolateral thoracotomy, a reduction in postoperative pain and analgesic requirements, as well as a more rapid recovery of pulmonary function with median sternotomy has been reported.[15]

Although this case represents only one CABG/LVRS without CPB, the fact that the patient developed the need for and required prolonged ventilatory support and eventually died due to pneumonia, underscores that these are very sick patients who have substantially reduced pulmonary reserve. With successful extubation of the patient in the operating room and a benign early post-operative course, it certainly appears that the beating heart approach for CABG may be advantageous in patients with very poor pulmonary function. In the combined CABG/LVRS study,[13] no data was given to permit evaluation of the time of extubation.

This patient is only the third LVRS patient reported in the literature to have a CABG concomitantly, and the first without the use of CPB. Although the patient died due to an

independent infection, CABG without CPB may be a viable option in those very high-risk patients with extremely poor pulmonary function who also have significant CAD not amenable to PTCA and whose lung deficiencies will not tolerate CPB.

References

1. Piehler JM, Trastek VF, Pairolero PC, *et al.* (1985). Concomitant cardiac and pulmonary operations. *J Thorac Cardiovasc Surg.* 90: 662-667.
2. Uhley Jr KS, Schmelzer V, Flege Jr JB, *et al.* (1992). Concomitant cardiac and pulmonary operation: the role of cardiopulmonary bypass. *Ann Thorac Surg.* 54: 289-295.
3. Yellin A, Moshkovitz Y, Simanski DA, and Mohr R. (1994). Coronary revascularization and pulmonary lobectomy without cardiopulmonary bypass. *J Thorac Cardiovasc Surg.* 108: 797-799.
4. Danton MHD, Anikin VA, McManus KG, *et al.* (1998). Simultaneous cardiac surgery with pulmonary resection: presentation of series and review of literature. *Izur J Cardio-Thorac Surg.* 13: 667-672.
5. Buffolo E, de Andrade JCS, Branco JN, *et al.* (1990). Myocardial revascularization without extracorporeal circulation. *Izur J Cardiothorac Surg.* 4: 504-508.
6. Ito H, Hamano K, Gohra H, *et al.* (1997). Relationship between respiratory distress and cytokine response after cardiopulmonary bypass. *Surg Today.* 27: 220-225.
7. Buffolo E, de Andrade CS, Branco JN, *et al.* (1996). Coronary artery bypass grafting without cardiopulmonary bypass. *Ann Thorac Surg.* 61: 63-66.
8. Naunheim KS, Fiore AC, and Wadley J, *et al.* (1988). The changing mortality of myocardial revascularization: Coronary artery bypass and angioplasty. *Ann Thorac Surg.* 46: 666-674.
9. Thurnheer R, Muntwhyler J, Stammberger U, *et al.* (1997). Coronary artery disease in patients undergoing lung volume reduction surgery for emphysema. *Chest.* 112: 122-128.
10. Canver CC, Bhayana JN, Lajos TZ, *et al.* (1990). Pulmonary resection combined with cardiac operations. *Ann Thorac Surg.* 50: 796-799.
11. Yokoyama T, Derrick MJ, Lee AW. (1993). Cardiac operation with associated pulmonary resection. *J Thorac Cardiovasc Surg.* 105: 912-917.
12. Rao V, Todd TRJ, Weisel RD, *et al.* (1996). Results of combined pulmonary resection and cardiac operation. *Ann Thorac Surg.* 62: 342-347.
13. Schmid RA, Stammberger U, Hillinger S, *et al.* (1999). Lung volume reduction surgery combined with cardiac interventions. *Izur J Cardio-Thorac Surg.* 15: 585-591.
14. Urschel HC, and Razzuk MA. (1986). Median sternotomy as the standard approach for pulmonary resection. *Ann Thorac Surg.* 41: 130-134.
15. Cooper JD, Nelems JM, and Pearson FG. (1978). Extended indications for median sternotomy in patients requiring pulmonary resection. *Ann Thorac Surg.* 26: 413-420.

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Calciphylaxis: A Review of Pathogenesis, Diagnosis and Treatment

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Abstract

Calciphylaxis is a rare but devastating complication of end-stage renal disease. The condition involves medial calcification within smaller blood vessels and subsequent intimal fibroelastic proliferation and stenosis. Although first described forty years ago, its etiology and pathogenesis are still incompletely understood. Hyperparathyroidism, hyperphosphatemia, an increased calcium-phosphate product, and exogenous agents including steroids, immunosuppressants, albumin, and blood products may all contribute to the development of calciphylaxis. The disease typically manifests as symmetrical, painful cutaneous nodules on the trunk and extremities progressing to livedo reticularis and eventually skin necrosis and ulceration. Ulceration of the digits, tongue, and penis, and involvement of the heart, nervous system, and gastrointestinal tract have been reported as well. Definitive diagnosis of calciphylaxis requires a skin biopsy. There is no proven treatment for the disorder, which carries a dismal prognosis. Patients frequently progress to infection of their skin ulcers, succumbing to overwhelming sepsis. Local wound care, subtotal parathyroidectomy, systemic antibiotics upon infection, and critical care support are the mainstays of therapy. Low calcium dialysis and hyperbaric oxygen therapy are newer, potential treatments. A recently derived mathematical formula attempts to predict, based on biochemical characteristics, which renal failure patients on dialysis are likely to develop the condition.

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Introduction

End stage renal disease of any etiology is associated with significant morbidity and mortality. Frequent complications include: hypertension, anemia, bone loss (as a result of secondary or tertiary hyperparathyroidism), electrolyte abnormalities including hyperkalemia and metabolic acidosis, and accelerated atherosclerosis. A far rarer complication arising in this setting, but one associated with a great deal of patient suffering is calciphylaxis, a disorder with a rapidly deteriorating course and a grave prognosis. This is a syndrome of ischemic tissue necrosis, primarily of the superficial skin, arising secondary to microvascular calcification, fibrosis, and luminal stenosis.[1,2] It is also known as calcific uremic arteriolopathy or uremic small vessel disease.[2]

Pathology

The characteristic lesion of calciphylaxis is calcification within the media of blood vessels, predominantly those in the range of 0.1 mm in diameter.[1] The calcifications have been described by some as consisting purely of calcium and phosphate crystals[2] while others have detected the presence of calcium, magnesium, and phosphate in variable stoichiometric relationships.[1] Superimposed upon this are intimal fibroblast deposition, fibroelastic proliferation, and luminal stenosis. Typically an area of perivascular necrosis is seen to accompany these lesions along with acute inflammatory changes. The lesions of calciphylaxis generally involve the skin, and thus manifest as necrosis of the epidermis, dermis, and subcutaneous tissue. These need to be distinguished from other, more common intravascular changes in uremic patients including atherosclerotic intravascular calcification, in which medial smooth muscle cell proliferation, macrophage invasion, and foam cells are present as well.[1]

Another uremic condition, Monckeberg's disease, also involves intravascular calcification although patients with this condition rarely develop clinical manifestations of tissue necrosis.[3-7]

Pathogenesis

The etiology and pathogenesis of calciphylaxis are incompletely understood. The term was coined in 1961 by Hans Selye, who described experimental soft tissue calcification in rats.[8] Selye exposed rats to various agents (vitamin D, phosphate, calcium salts, and parathyroid hormone [PTH]) in a process he termed "sensitization." A day later the rats were injected with iron salts, egg albumin, polymyxin, or 5-hydroxytryptamine in a process termed "challenging." The rats developed soft tissue calcification, although importantly, no intravascular calcification was noted.[1,2,7] Equating the two-step sensitization and challenging process to anaphylaxis, Selye coined the term "calciphylaxis." Selye's concept differs from the modern view of calciphylaxis, which refers to intravascular calcification, endovascular fibroelastic proliferation, and tissue necrosis, but not to extravascular soft tissue calcification. Current theories regarding the pathogenesis of this disorder postulate a mechanism whereby hyperparathyroidism, a high phosphate level, and a high calcium: phosphate ratio in the setting of uremia predispose patients to the development of intravascular calcification.[1] Although not proven, exposure to various agents including steroids, immunosuppressants, albumin, blood products, and exogenous vitamin D and calcium carbonate has been implicated in the precipitation of these deposits.[9-11] However, this proposed mechanism cannot completely account for the pathogenesis of calciphylaxis since elevated calcium, phosphate, calcium phosphate, or PTH levels is neither necessary nor sufficient to develop or diagnose the condition.[1,2,6] Furthermore, evidence supporting a correlation between these biochemical parameters and the development of calciphylaxis remains inconclusive.[12] Complicating the picture further is the finding that calciphylaxis does not develop solely in the uremic state, nor does it arise strictly in dialysis patients.[1,13] The disorder has been reported in patients without end-stage renal disease whose underlying illness was primary hyperparathyroidism or hypercalcemia of malignancy.[1,13]

Additional models have suggested a relationship between calciphylaxis and the use of warfarin anticoagulation, while others have proposed that a high dose of calcium carbonate used as a gastrointestinal phosphate binding agent promotes the condition.[2,14] Obesity, hypoalbuminemia, and a longer duration of hemodialysis have also been shown to be independently associated with the development of calciphylaxis.[12,15] Finally, there have been several reports of mild to severe deficiency in the intrinsic anticoagulation factors protein C and S among patients developing calciphylaxis, suggesting that fluctuations in these factors, or an inherited thrombogenic predisposition, may render patients susceptible to the condition.[2,7]

Epidemiology

Among hemodialysis patients, calciphylaxis is estimated to occur at an incidence of 1% per year. Unfortunately, the incidence in the entire chronic renal failure population is unknown.[3,16] The prevalence of the disease has been reported at 4.1%.[12] However, calciphylaxis is highly underreported in the literature with fewer than two hundred cases published since the concept was introduced. The disease has been reported predominantly in adult patients between the ages of 18 and 83.[1,7] There is no clear increased prevalence in any particular ethnic group.[12,15] The disease appears to occur more commonly in females, with female to male ratios between 1.5 to 1 and 4 to 1 having been reported in various studies.[2,12,15,17]

Etiology

End stage renal disease is responsible for 90% of reported cases of calciphylaxis.[1] The underlying etiology of the renal disease in these patients is varied and includes diabetes mellitus, hypertensive nephrosclerosis, chronic interstitial nephritis, polycystic kidney disease, and various glomerulonephritides. Eight percent of reported patients developed the condition due to primary hyperparathyroidism and 2% in the setting of hypercalcemia of malignancy.[1,13]

Clinical Presentation and Disease Manifestations

Patients developing calciphylaxis undergo a rather typical progression of events.[1,2,12,17] During onset, extremely painful cutaneous nodules develop, which may be intensely pruritic. These most commonly involve the skin of the trunk and proximal lower extremities symmetrically although distal lower extremity and upper extremity disease are frequent as well; involvement of the head is rare. The lesions progress to a diffuse, violacious, lace-like and mottled pattern termed livedo reticularis. Involved areas undergo superficial skin necrosis to form large ulcerations, which may become infected and gangrenous. These ulcers resemble burn wounds and are highly prone to infection. Infrequently the ulcers will invade deeper than the superficial skin to involve underlying skeletal muscle.[1] Subsequently, patients often develop wound infection and sepsis, which are usually refractory to antibiotics and intensive care unit support. A second common manifestation of calciphylaxis is acral ulceration and gangrene progressing to autoamputation.[2]

The superficial lesions of calciphylaxis have also been described on the prepuce and glans penis, with progress on to painful ulceration, infection, and gangrene necessitating debridement and at times penectomy.[2,14,18,19] Involvement of the tongue requiring a hemiglossectomy has been reported.[6] Cardiovascular complications include a rapid onset of aortic valve and ascending aorta calcification,[20] mitral valve calcification and thickening with calcific plaque embolization to the cerebral circulation causing a stroke,[21] and myocardial dysfunction secondary to intramyocardial calcification in patients with systemic lupus erythematosus and end-stage renal disease.[22] Colonic ischemic necrosis resulting in gastrointestinal hemorrhage,[2,5] ischemic myopathy mimicking dermatomyositis,[3] polyneuropathy,[13] ischemic optic nerve atrophy,[1] and corneal and conjunctival

calcinosis have all been described as well. In many of these reports surgical resection and autopsy revealed calciphylaxis in the diseased organs and tissues, suggesting that calciphylitic events were responsible for organ dysfunction.

Diagnosis

The presence of calciphylaxis is not accurately predicted by biochemical laboratory parameters.[1] Several case reports and retrospective case studies suggest a correlation of calciphylaxis with serum calcium, phosphate, calcium phosphate product, PTH, or alkaline phosphatase (ALP) levels.[12,15,17] However, there are several reports of patients developing calciphylaxis without an abnormality in these values.[2,7,15] Furthermore, although in most cases PTH and phosphate levels tend to be elevated, both these markers are highly non-specific in the setting of chronic renal failure and end-stage renal disease.

While useful biochemical parameters remain elusive, radiological investigations may suggest the presence of calciphylaxis. Frequently a non-specific, stippled pattern of vascular calcification is observed on plain film radiographs along with metastatic soft tissue calcification.[1] The presence of calcifications less than 0.5 mm in width on these radiographs may be more specific for the presence of calciphylaxis.[1] Nonetheless, a tissue biopsy from a site of cutaneous involvement demonstrating the pathology described above is necessary to confirm the diagnosis.

Differential Diagnosis

The differential diagnosis of calciphylaxis may be broad and depends in part on the stage of the disease at presentation.[1,23,24] Important considerations are vasculitides, warfarin-induced skin necrosis with recently intiated warfarin therapy, cellulitis or necrotizing fasciitis, atheroembolic diseases including peripheral vascular disease and cholesterol emboli, endocarditis, cryofibrinogenemia, pyoderma gangrenosum, and superficial thrombophlebitis.

Treatment

There is no clinically proven, completely effective treatment for calciphylaxis. Most suggested therapies have been tried on only a small number of patients and therefore their efficacies are not fully established. The treatment approach consists of supportive, symptomatic care of the severely painful and disfiguring lesions and an attempt at cure. Supportive care involves stepwise increase in analgesic medication, aggressive skin wound management through cleaning, debridement and split-thickness skin grafting, and the administration of antibiotics upon infection.[11,12,17,25] The use of prophylactic antibiotics has not been reported. Supportive care through resuscitation and aggressive life support for the cardiac, gastrointestinal, and systemic complications may also be required as the disease progresses. Amputation of an extremity, and in rare cases resection of the bowel, tongue, penis, or other involved organ may be necessary.[2,5,6,11,18,19]

Subtotal parathyroidectomy is often attempted as a therapeutic procedure. Its usefulness is questionable given that assessments of the effectiveness of this procedure is limited to case series and retrospective chart reviews.[1] The value of parathyroidectomy is particularly unclear when PTH levels are not elevated and performing this procedure in this setting may lead to deleterious induction of low turnover bone disease.[17,26,27]

Kane *et al.* described three patients with calciphylaxis who developed the typical severe superficial skin ulcers and underwent parathyroidectomy.[17] All demonstrated complete or near-complete healing of the wounds within several months, with no recurrence. Similarly, 8 of 10 patients in the series reported by Angelis *et al.* underwent parathyroidectomy for calciphylaxis related lesions with subsequent resolution of pain and ulcers over the next several months.[12] Chan *et al.* found no survival benefit with parathyroidectomy in a series of 47 patients.[28] Unfortunately, it is difficult to comprehensively evaluate the effectiveness of parathyroidectomy on the basis of such limited case series. In the only available large, retrospective review of parathyroidectomy in the setting of calciphylaxis, Hafner *et al.* analyzed the literature to find reports of hemodialysis patients with calciphylaxis who did or did not undergo parathyroidectomy.[7] Sixty six percent of the 58 patients who underwent parathyroidectomy survived, as opposed to a 35% survival among the 37 patients those who did not receive surgery. The range of survival among parathyroidectomy patients was 2 weeks to 21 months (no mean survival was established) while those not undergoing the procedure had a survival range of several days to 2 years. Unfortunately, this study had many limitations including its retrospective nature, reliance upon a literature replete with small series and case reports spanning decades, lack of clarity regarding the actual mean and median survival benefits conferred by parathyroidectomy, and a heterogeneous population. Therefore, the benefits conferred by parathyroidectomy in these patients remain uncertain, particularly when PTH levels are not elevated. Performing the procedure in this setting may lead to deleterious induction of low turnover bone disease. Nevertheless, one author has proposed prophylactic parathyroidectomy in patients with elevated PTH and radiographic evidence of vascular calcification.[29]

Several authors also suggest the discontinuation of sensitizing and precipitating agents if clinically possible. These include steroids, immunosuppressant and immunotoxic agents, albumin, blood products, iron injections, and high doses of calcium carbonate and vitamin D derivatives.[9-11] It must, however, be remembered that none of these agents has definitively been shown to cause onset or progression of calciphylaxis. These medications may be essential in controlling the underlying systemic illness causing the renal disease or a secondary unrelated condition. Therefore, a cost-benefit analysis considering the impact of withdrawing such medications as immunosuppressants and immunotoxic

agents (in patients with autoimmune disorders, for example) must be performed before such treatment is withheld in the hope of improving the course of calciphylaxis.

New innovative treatments include the use of low calcium dialysis. In one case report by Lipsker *et al.*, a 46 year old male with renal failure secondary to amyloidosis developed the cutaneous manifestations of calciphylaxis (proven with biopsy).[30] Use of low calcium dialysis was followed by cessation of wound progression in 1 week, wound regression in 6 weeks, and recovery in 3 months. Two authors have reported the use of hyperbaric oxygen therapy in patients with calciphylaxis refractory to medical and surgical therapy.[31,32] In both reports, patients' wounds healed completely following 7 to 8 weeks of hyperbaric oxygen therapy. The high oxygen tension may function to promote angiogenesis in the region of skin necrosis, thereby increasing the number of patent blood vessels and promoting regeneration of the destroyed tissue. Low molecular weight heparin and bisphosphonates are other treatment modalities that have been considered although neither has been extensively tested or tried clinically.[33,11]

There is one report of a 60 year old female with chronic renal failure and cutaneous manifestations of calciphylaxis which were refractory to phosphate binders, low phosphate diet, low calcium dialysis, and parathyroidectomy, but resolved with a course of 10 days of oral prednisone (40 mg twice daily) followed by 3 months of oral cimetidine (300 mg twice daily).[34] It is uncertain what role cimetidine or prednisone had in improving the manifestations of calciphylaxis in this patient. Furthermore, although cimetidine is believed to have some immunomodulatory properties, it is entirely unclear by what mechanism the medication may exert a beneficial effect in calciphylaxis.[34] The only rationale for this intervention was a previous report of successfully treating a different condition involving inflammation of subcutaneous blood vessels, termed fasciitis-panniculitis syndrome, using oral prednisone and cimetidine.[34,35]

Prognosis

Patients developing calciphylaxis have a poor prognosis regardless of the treatment modalities used. Overall mortality is estimated at 60 to 90%, the usual etiology being sepsis from wound infections.[1,2] Even with parathyroidectomy and aggressive life support, patients on average do not survive longer than several months.[7] It is also difficult to predict who will improve with medical or surgical therapy, as outcome does not correlate well with pretreatment biochemical parameters.[7] In general, the prognosis is considered poorer if there is trunk or proximal limb involvement as opposed to distal extremity involvement alone.[1,2,7,28] Patients who are discovered to have the disease earlier may receive medical and surgical intervention prior to the development of severe ulceration and tissue destruction. In theory, this should decrease the likelihood of developing large infection-prone ulcerations and cutaneous and visceral ischemia, but the benefit of early intervention in decreasing morbidity and mortality is not established.

Levin *et al.* attempted to derive a mathematical model to identify patients at risk of developing calciphylaxis.[16] A multivariate regression analysis was not possible due to the rarity of the condition. Instead the authors derived an arithmetic model based on physiological reasoning, clinical observations, and a literature review of chronic dialysis patients (excluding those with diabetes, systemic lupus erythematosus, and renal transplant). The derived model is an expression: 2 x [(Calcium x Phosphate)-5] x ALP x PTH ratio. The calcium and phosphate units are in millimoles per litre, ALP is in international units (IU) and the PTH ratio is the measured PTH value divided by the upper limit of normal for PTH at the reporting laboratory. Values greater than 1000 were considered high risk for developing calciphylaxis. The model attempts to incorporate several commonly abnormal biochemical parameters in calciphylaxis in order to increase specificity (given that individual parameters can be abnormal in many patients with renal disease). At the same time it emphasizes the importance of the calcium phosphate product (if the product is less than 5 the result will be negative, immediately rendering the patient low risk).

When the model was tested on a separate group of patients, sensitivity was found to be 80% and specificity 92%. The positive predictive value was 66% and negative predictive value 96% (as can be expected in a disease with low prevalence). Clearly, this model contains several limitations. Patients with common diseases (diabetes, systemic lupus erythematosus) were excluded, derivation and testing samples were small, and testing of the model used retrospective data. Nevertheless, it does offer a starting point for trying to identify and potentially treat patients at risk for developing this devastating disease.

Conclusion

Calciphylaxis is a relatively rare complication of end stage renal disease. However, when the disease does develop it imposes a tremendous burden and suffering on patients and almost invariably carries a dismal prognosis. Depending on its presentation, the disease may also pose a diagnostic or therapeutic challenge to various medical and surgical specialties. Given the underreporting of calciphylaxis, the incomplete understanding of its pathogenesis, and the fact that current treatment options do not prolong life significantly, increasing awareness of the disease is necessary to promote future basic science research and prospective clinical trials in medical and surgical management.

References

1. Fischer AH and Morris DJ. (1995). Pathogenesis of calciphylaxis: Study of three cases with literature review. *Hum Pathol.* 26:1055-1064.
2. Coates T, Kirkland GS, Dymock RB, *et al.* (1998). Cutaneous necrosis from calcific uremic arteriolopathy. *Am J Kidney Dis.* 32:384-391.
3. Flanigan KM, Bromberg MB, Gregory M, *et al.* (1998). Calciphylaxis mimicking dermatomyositis: Ischemic myopathy complicating renal failure *Neurology.* 51:1634-1640.
4. Mehta RL, Scott G, Sloand JA, and Francis CW. (1990). Skin necrosis associated with acquired protein C deficiency in patients with renal failure and calciphylaxis. *Am J Med.* 88:252-257.

Burns DK (1998). Systemic calciphylaxis with fatal massive gastrointestinal hemorrhage. *Arch Pathol Lab Med.*

RM, Gutierrez JL, and Mayorga L. (1997). Calciphylaxis causing tongue necrosis: A case report. *J Oral Maxillofac Surg.* 55:193-196.

J, Keusch G, Wahl K, *et al.* (1995). Uremic small artery disease with medial calcification and intimal hyperplasia (so called calciphylaxis): A complication of chronic renal failure and benefit from parathyroidectomy. *J Am Acad Dermatol.* 33:954-962.

8. Selye H. (1962). *Calciphylaxis.* University of Chicago Press: Chicago.
9. Campistol JM, Alnurall J, Martin E, *et al.* (1989). Calcium carbonate induced calciphylaxis. *Nephron.* 51:549-550.
10. Worth RL. (1998). Calciphylaxis: Pathogenesis and therapy. *J Cut Med Surg.* 2:245-248.
11. Gilson RT and Milum E. (1999). Calciphylaxis: Case report and treatment review. *Cutis.* 63:149-153.
12. Angelis M, Wong L, Myers SA, and Wong LM. (1997). Calciphylaxis in patients on hemodialysis: A prevalence study. *Surgery.* 122:1083-1090.
13. Buxtorf K, Cerottini JP, and Panizzon RG. Lower limb skin ulcerations, intravascular calcifications, and sensorimotor polyneuropathy: Calciphylaxis as part of a hyperparathyroidism? *Dermatology.* 198:423-425.
14. Handa SP and Strzelczak D. (1998). Uremic small artery disease: Calciphylaxis with penis involvement. *Clin Nephr.* 50:258-261.
15. Blever A, Choi M, Igwemezie B, *et al.* (1998). A case control study of proximal calciphylaxis. *Am J Kidney Dis.* 32:376-383.
16. Levin A, Mehta RL, and Goldstein MB. (1993). Mathematical model to help identify the patient at risk of ischemic tissue necrosis – a potentially lethal complication of chronic renal failure. *Am J Nephrol.* 13:448-453.
17. Kane WJ, Petty PM, Sterioff S, *et al.* (1996). The uremic gangrene syndrome: Improved healing in spontaneously forming wounds following subtotal parathyroidectomy. *Plast Reconstr Surg.* 98:671-678.
18. Jhaveri F, Woosely JT, and Fried FA. (1998). Penile calciphylaxis: Rare necrotic lesions in chronic renal failure patients. *Clin Urol.* 160:764-767.
19. Wood JC, Monja M, and Hellstrom WJ. (1997). Penile calciphylaxis. *Urology.* 50: 622.
20. Asirvatham S, Sebastian C, Sivaram CA, *et al.* (1998). Aortic valve involvement in calciphylaxis: Uremic small artery disease with medial calcification and intimal hyperplasia. *Am J Kidney Dis.* 32:499-502.
21. Katsamakis G, Lukovits TG, and Gorelick PB. (1998). Calcific cerebral embolism in systemic calciphylaxis. *Neurology.* 51:295-297.
22. MacLean C and Brahn E. (1995). Systemic lupus erythematosus: Calciphylaxis induced cardiomyopathy. *J Rheumatol.* 22:177-179.
23. Melikoglu M, Apaydin S, Hamuryudan V, *et al.* (1996). Calciphylaxis: A condition mimicking necrotizing vasculitis. *Clin Rheumatol.* 15:498-500.
24. Sankarasubbaiyan S, Scott G, and Holley JL. (1998). Cryofibrinogenemia: An addition to the differential diagnosis of calciphylaxis in end-stage renal disease. *Am J Kidney Dis.* 32:494-498.
25. Loynes JT. (1999). A rare cause of breast necrosis. *Postgrad Med.* 106:161-62.
26. Kent RB and Lyerly RT. (1994). Systemic calciphylaxis. *South Med J.* 87:278-281.
27. Budisavijevic MN, Cheek D, and Ploth DW. (1995). Calciphylaxis in chronic renal failure. *J Am Soc Nephrol.* 7:978-982.
28. Chan YL, Mahony JF, Turner JJ, *et al.* (1983). The vascular lesions associated with skin necrosis in renal disease. *Br J Dermatol.* 109:85-95.
29. Torok L and Kozepessy L. (1991). Uremic gangrene syndrome. *Acta Dermatol Venereol.* 71:455.
30. Lipsker D, Chosidow O, Martinez F, *et al.* (1997). Low-calcium dialysis in calciphylaxis. *Arch Dermatol.* 133:798-799.
31. Vassa N, Twardowski ZJ, and Campbell J. (1994). Hyperbaric oxygen therapy in calciphylaxis-induced skin necrosis in a peritoneal dialysis patient. *Am J Kidney Dis.* 23:878-881.
32. Dean SM and Werman H. (1998). Calciphylaxis: A favourable outcome with hyperbaric oxygen. *Vasc Med.* 3:115-120.
33. Perez-Mijares R, Guzman-Zamudio JL, Payan-Lopez J, *et al.* (1996). Calciphylaxis in a hemodialysis patient: Functional protein S deficiency? *Nephrol Dial Transplant.* 11:1856-1859.
34. Elamin EM and McDonald AB. (1996). Calcifying panniculitis with renal failure: A new management approach. *Dermatology.* 192:156-159.
35. Naschitz JE, Yeshurun D, Zuckerman E, *et al.* (1992). The fasciitis-panniculitis syndrome: clinical spectrum and response to cimetidine. *Sem Arthrit Rheum.* 21:211-220.

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Epileptic Seizures: Do They Cause Reproductive Dysfunction?

Heather E. Edwards, Ph.D. (0T2), Neil J. MacLusky, Ph.D.,† and W. McIntyre Burnham, Ph.D.*

Abstract

Reproductive dysfunction and endocrine disorders are common among women and men with epilepsy, in particular, with temporal lobe epilepsy. The relative contribution of seizures versus anticonvulsant drugs on reproductive dysfunction, however, is not clear. Studies in rodents indicate that both focal limbic seizures and primary generalized seizures can directly contribute to reproductive dysfunction. Both types of seizures disrupt normal ovarian cyclicity in females. Limbic seizures also cause the development of polycystic ovaries and premature aging of the hypothalamic-pituitary neuroendocrine axis. In male rodents, repeated generalized seizures result in transient hypogonadism (i.e., decreased serum androgens and lowered gonadal tissue weight), while focal limbic seizures facilitate the development of hypergonadism (increased gonadal function). Such seizure-induced alterations in gonadal hormone secretion may further enhance or suppress limbic seizure activity, depending on resultant serum levels of estrogen, progesterone and/or androgens. Studies in rodents suggest that reproductive dysfunction in women and men with epilepsy might result from seizure-related interference with the normal functions of the hypothalamic-pituitary-gonadal axis.

Introduction

Epilepsy affects approximately 1% of the general population, often initially appearing during childhood and requiring long-term therapeutic control. Reproductive dysfunction and endocrine disorders among persons with epilepsy are unusually common, being estimated at about 50%. Reduced fertility,[1] diminished sexual desire,[2] and diminished sexual responsiveness[3] have all been described. Menstrual disorders including anovulatory cycles, irregular menstrual cycle length and amenorrhea, as well as endocrine disorders such as hypogonadotropic hypogonadism, functional hyperprolactinemia and polycystic ovarian disease are all overrepresented in women with epilepsy.[4-7] Men with epilepsy appear to have an increased risk of developing erectile dysfunction, hyperprolactinemia, and hyper- or hypogonadism.[8-10] In addition, over 90% of men with epilepsy have abnormal semen analysis, including decreased sperm count, abnormal morphology, and impaired motility.[11] These factors may contribute to the observation that men with idiopathic epilepsy are only 36% as likely as male unaffected siblings to ever father a pregnancy.[12]

Such clinical observations of an interaction between seizures and hormones provide the rationale for investigations in animal seizure models. This paper first introduces the reader to pathways linking seizure activity as well as antiepileptic drug medication to changes in reproductive function. Results of experiments performed in rats are reviewed, with comparisons made against clinical observations in humans. Lastly, the article discusses how the development of reproductive disorders can further enhance, or in some cases attenuate, seizure activity.

Reproductive Dysfunction – The Temporolimbic Connection

Reproductive dysfunction is more common in patients with

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temporal lobe epilepsy than with generalized seizures or epilepsies originating in other regions of the brain.[13] This may relate to the extensive interconnections between limbic structures of the temporal lobe, such as the hippocampus and amygdala, and the hypothalamic nuclei which govern the regulation, production, and secretion of gonadotrophin releasing hormone (GnRH) (Figure 1).[14] Neurological impairments that give rise to epileptic seizures in the limbic system may therefore contribute to alterations in the pattern of pulsatile release of GnRH.[15] Altered frequency or amplitude of GnRH would secondarily affect the release of pituitary gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH), thereby giving rise to endocrine disorders. Clinical studies support the hypothesis that seizures in the temporal lobe directly alter gonadotropin secretion. Bilo *et al.* reported that drug-free epileptic women had higher LH pulse frequencies than normal controls.[16]

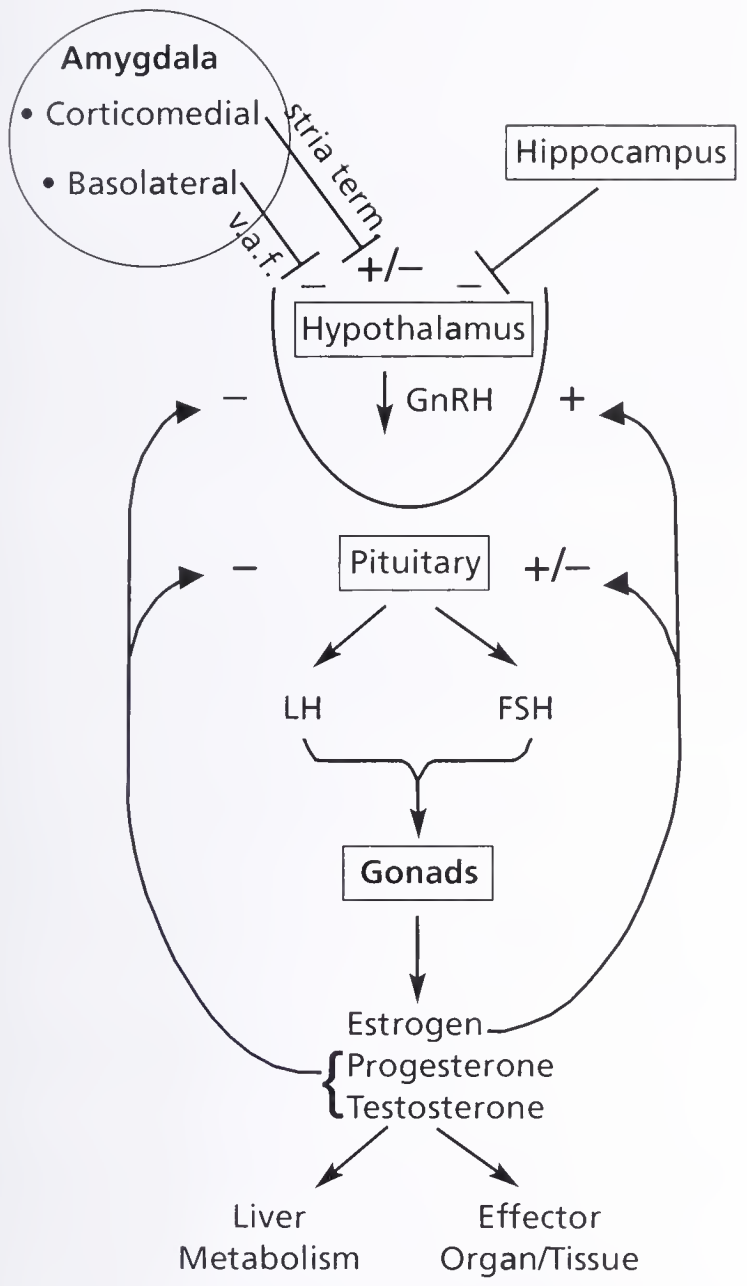

Figure 1. *Diagram of the hypothalamic-pituitary-gonadal axis and its modulation by limbic structures. Note the two functionally distinct regions of the amygdala. Connections are designed as predominantly excitatory (+), inhibitory (–), or in some cases, both (+/–). GnRH, gonadotropin releasing hormone; LH, luteinizing hormone; FSH, follicle stimulating hormone; stria term, stria terminalis; v.a.f., ventral amygdalofugal pathway.*

Dana-Haeri *et al.* also reported postictal (i.e., post-seizure) elevations of LH in women and men whose seizures involved the temporal lobe.[17]

How limbic seizures alter endocrine function is not known. Theoretically, seizure-induced increases in GnRH pulse frequency would favor LH biosynthesis over FSH, giving rise to an increased serum LH/FSH ratio – a profile consistent with the development of polycystic ovaries (Figure 2).[18] Conversely, decreased GnRH secretion and hence, a decrease in the LH/FSH ratio, is consistent with the development of hypogonadotropic hypogonadism (i.e., decreased gonadal function as a result of reduced hypothalamic-pituitary gonadotropin secretion).[6,13,15] Seizure induced excesses of GnRH secretion could also cause desensitization of the hypothalamic-pituitary system and suppress the release of gonadotropins LH and FSH by the anterior pituitary.[19,20] The net result is anovulatory cycles in females and hypogonadism in males.[5] The ability of excess GnRH to shut down gonadal function provides the basis for use of synthetic GnRH therapy in women with catamenial epilepsy to control for hormone-related increases in seizure activity.[21]

The nature of the endocrine disorder in epileptic persons may depend on the precise location of the epileptic focus, since there are functional distinctions between the different limbic efferent pathways on GnRH secretion. As illustrated in Figure 1, the hippocampus has efferent connections via the fornix with the arcuate and ventromedial nuclei of the hypothalamus, and is known to exert an inhibitory effect on gonadotropin secretion.[22] By contrast, the amygdala has two functional divisions that exert opposing influences on hypothalamic gonadotropin secretion: (1) The ventral amygdala (basolateral nuclei) projects efferents to the lateral hypothalamus via the ventral amygdalofugal pathway. It is thought to exert a suppressive effect over gonadotropin secretion, since stimulation of that pathway inhibits gonadotropin release and ablation augments it.[23] (2) The medial amygdala (corticomedial nuclei) connects via the stria terminalis to the septum, preoptic area and the external border of the hypothalamic ventromedial nuclei.[24] Efferents of the corticomedial amygdala appear mixed and can both inhibit or facilitate gonadotropin secretion.[25,26]

Observations of persons with paroxysmal temporal lobe epilepsy also suggest that the consequences of a temporal lobe lesion may be lateralized.[27,28] In women with unilateral temporal lobe interictal epileptiform discharges, there was a strong predominance of left-sided discharges with enhanced LH pulse frequency and the development of polycystic ovarian disease.[28] In contrast, right-sided discharges were associated with reduced LH pulse frequency and the development of hypogonadotropic hypogonadism.[28] In men, the opposite scenario appears to be true. There is an association between left-sided interictal discharges and a *decrease* in LH

pulse frequency as compared to men with right-sided disease.[29] Thus, lateralized hypothalamic asymmetries may explain, at least in part, the occurrence of hyper- versus hypo-gonadotropic hypogonadism in persons with epilepsy.

Like the human, studies indicate that the rodent brain is lateralized in function; although the extent of phylogenetic similarity is not known. In the rat, seizures in the right amygdala significantly increase fear responses (i.e. defensive behavior and stress-induced enhancement of the startle response).[29] In contrast, seizures in the left amygdala increase aggression and predatory attack behavior.[29] While behavioural changes in response to seizures appear to be lateralized, it is not known whether seizure-induced changes in reproductive function are lateralized in the rat. These studies are currently under investigation.

Role of Anti-Epileptic Drugs

Relationships between seizure type, seizure frequency and type of endocrine disorder in patients with epilepsy have been difficult to determine due to the confounding effects of anti-epileptic drugs.[30] Some drugs (i.e., phenytoin, barbiturates) increase the metabolic clearance rate of the gonadal steroids through induction of hepatic microsomal oxidative enzyme activity.[31,32] The cytochrome P450 system is shared by these drugs and the steroid hormones. These drugs also increase concentrations of sex hormone-binding globulin, which binds circulating gonadal steroids.[22,30] The net result is a lower amount of free, biologically active hormone in the circulation which, in turn, would alter the hormonal feedback regulation of pituitary gonadotropins, LH and FSH.[31,33] As well, rapid clearance of the steroid hormones may lower their levels below what is needed for hypothalamic and pituitary inhibition, thereby allowing ovulation to occur.[34] This might explain, at least in part, the four-fold increase in incidence of unplanned pregnancies in women receiving anti-epileptic drugs.[35]

Other drugs, including sodium valproate, the benzodiazepines and vigabatrin, affect circulating steroid hormone concentrations more directly by decreasing GnRH release through enhanced GABAergic input to the GnRH neurons.[36,37] Phenobarbital, carbamazepine and phenytoin have also been shown to directly alter the sensitivity of pituitary gonadotrophins to stimulation by GnRH.[38-40] Thus, some anti-epileptic drug medications may themselves contribute to the development of reproductive abnormalities.

Medications might also have a direct effect on gonadal function. For example, spermatogenesis is sensitive to a variety of factors (temperature, diet, alcohol, stress) including drugs. Antiepileptic drugs such as carbamazepine and phenytoin have been shown to directly inhibit testosterone production by the Leydig cells *in vitro*.[41] These *in vitro* studies demonstrated a differential effect by each of the anti-epileptic drugs on the metabolic pathway of sex steroid hormones.[41]

Lastly, Isojarvi and coworkers[42] present compelling evidence to suggest that valproate use is associated with a higher occurrence of polycystic ovarian disease. They suggest that the overrepresentation of polycystic ovarian disease among long-term valproate-treated women with epilepsy may be attributable to valproate-induced weight gain and the development of insulin resistance characterized by hyperinsulinemia and decreased insulin-like growth factor-binding protein and sex hormone-binding globulin. Such endocrine changes lead to ovarian hyperstimulation, with the net result being hyperandrogenism and structural changes characteristic of polycystic ovaries. In stark contrast, however, Herzog and coworkers[43] showed that polycystic ovaries were more common among the untreated (30%) than the drug-treated (13%) women with epilepsy. Thus, although anti-epileptic drugs alter reproductive hormone levels, it is unlikely that drug effects alone can explain all of the reproductive endocrine disorders among women with epilepsy.

Do Seizures Affect Reproductive Function? Evidence from Animal Experiments

Clinically, it is difficult to know whether reproductive dysfunction occurs as a result of the seizures themselves, the anti-epileptic drug medication, or both. This problem can be circumvented by use of animal models, in which the effects of the seizures can be examined under more controlled conditions.

Role of Limbic Seizures

Studies in animals have provided evidence consistent with the hypothesis that limbic seizures interfere with the regulation of reproductive function. In adult female rats, repeated daily convulsions via treatment with chemicals such as flurothyl,[44] kainic acid[45] or pilocarpine[46] can disrupt reproductive function, at least temporarily. Resection of both amygdalae leads to degeneration of spermatic tubules and aspermatogenesis in male rats and cats,[47,48] and causes anovulatory cycles and polycystic ovary changes in female dermice.[6] Bilateral temporal lobectomies in female monkeys produce prolonged disruptions in menstrual cyclicity[49] and can result in the Kluver-Bucy syndrome, characterized by uninhibited sexuality.[50] Similar changes in sexual behavior arise in laboratory monkeys with bilateral removal of the amygdala alone.[51] Thus, limbic dysfunction appears to lead to reproductive dysfunction.

More recent studies in our laboratory have reported a direct effect of limbic seizures on reproductive function using the amygdala kindling model in both the adult female and male rat. The kindling model is the best known animal model of complex partial seizures and involves

repeated, brief electrical stimulations of the brain, usually limbic sites, using a bipolar electrode.[52,53] At first, epileptiform afterdischarges are localized to the site of stimulation and do not propagate to other parts of the brain.[53] With repeated stimulation, focal seizure threshold drops and seizures secondarily generalize to other brain regions, eventually leading to the onset of behavioral convulsions.[52] Results of our studies are presented in Table 1.

We have reported that, in female rats, repeated kindled seizures in the right basolateral amygdala cause the cessation of regular estrous cycles, the development of polycystic ovaries, and premature reproductive aging of the hypothalamic-pituitary neuroendocrine axis.[54] As a result, the hypothalamus and pituitary become refractive to exogenous hormone manipulation and functionally lose their ability to support ovulation.[54] At the level of the ovary, follicles failed to rupture and corpora lutea did not develop, resulting in chronic high serum levels of estrogen.

Unopposed estrogen in the female rat has deleterious effects on neurons in the arcuate nucleus of the hypothalamus, causing degeneration of axons, axon terminals and dendrites.[55,56] It also changes hypothalamic sensitivity to ovarian steroids[57] and alters the catecholaminergic and adrenergic regulation of the suprachiasmatic nucleus - thought to be the master circadian pacemaker of the hypothalamus.[58,59] The net result is an alteration in hypothalamic regulation of GnRH secretion and LH synthesis, storage and/or release.[60] These changes lead to perturbations in reproductive cyclicity. Taken together, the neuroendocrine impairment observed in kindled female rats is likely the result of a number of convergent mechanisms, including the excessive neural activity associated with seizures, as well as the effects of chronic exposure to elevated serum estrogen.

In male rats, amygdala kindling caused the development of a hypergonadal state, characterized by increased testis, epididymis and pituitary weight, as well as increased serum testosterone, estrogen and prolactin levels.[61] Increased serum estrogen levels were particularly intriguing, since estrogen levels are not normally detectable in the serum of male rats. Chronic elevation of serum estrogen might be responsible for the observed increase in pituitary weight and hyperprolactinemia, since estrogen (at least 1 week of exposure) is known to stimulate pituitary lactotroph hyperplasia and prolactin secretion.[62] Clinical studies similarly report that serum estrogen levels are frequently elevated in men with temporal lobe epilepsy that are not receiving drug medication,[13] although the mechanism of this is not clear.

High serum levels of testosterone and estrogen in kindled male rats should exert negative feedback effects on both the hypothalamus and pituitary to inhibit GnRH release; hence, decreasing testicular steroid production. These feedback control mechanisms do not appear to be operating normally in kindled male rats, since testicular weight and serum testosterone and estrogen levels all remain high 24 h after the last kindled seizure.[61] Why feedback regulation is impaired is not entirely clear. Data in our laboratory suggests that seizures up-regulate androgen receptors, and possibly estrogen receptors, around the seizure focus (unpublished observations).

Table 1
Effect of Seizures on Parameters of Reproductive Functions

	Estrous Cycles	Gonadal Tissue	Serum Hormones	Neuroendrocrine Impairment?	References
Females					
Right Amygdala Kindled Seizures	Stops cycle	Delvelop polycystic ovaries	Increased estrogen, and prolactin. Low progestin levels	Yes	Edwards et al.[54]
Electroconvulsive Shock Seizures	Delays pubertal onset of cycles	—	Increased prolactin. levels	Yes	Bhanot R, Wilkinson M.[44] Carson RC, Wilkinson M.[68] Bhanot R, Wilkinson M.[69]
Males					
Right Amygdala Kindled Seizures		Increased testis, epididymis, and pituitary weight	Increased testosterone, estrogen and prolactin	Yes	Edwards et al.[61]
Repeated maximal Electroconvulsive Shock Seizures	—	Short-term decrease in testis, epididymis, and prostate weight	Tansient decrease in testosterone, but long-term increase in estrogen and prolactin	Transient, if any	Edwards et al.[61]

No studies to date, however, have investigated the effects of limbic seizures on steroid hormone receptor levels in the hypothalamus or pituitary. As mentioned previously, impaired negative feedback at the level of the hypothalamus might be the result of unopposed estrogen, since chronic estrogen causes degeneration of axons, axon terminals and dendrites in the arcuate nucleus[55,56] as well as alters feedback sensitivity to circulating steroid hormones.[57] Taken together, repeated limbic seizures appear to cause neuroendocrine impairment of the hypothalamic-pituitary-gonadal axis in male rats.

While the underlying mechanisms for limbic seizure-induced reproductive dysfunction remain to be elucidated, there are a number of likely possibilities. Right amygdala-kindled seizures in both the male and female rat may increase pulsatile GnRH release[63,64] thereby favoring pituitary LH biosynthesis over FSH (Figure 2). Such an increase in the LH/FSH ratio would facilitate development of polycystic ovaries in females. In males, an elevated LH/FSH ratio would stimulate testicular Leydig cell production of testosterone – a hormone vital for the initiation of sperm production.[65,66] Unabated LH would also cause Leydig cell and Sertoli cell proliferation and/or hypertrophy,[67] accounting for the increase in testicular weight noted in kindled subjects (Table 1).

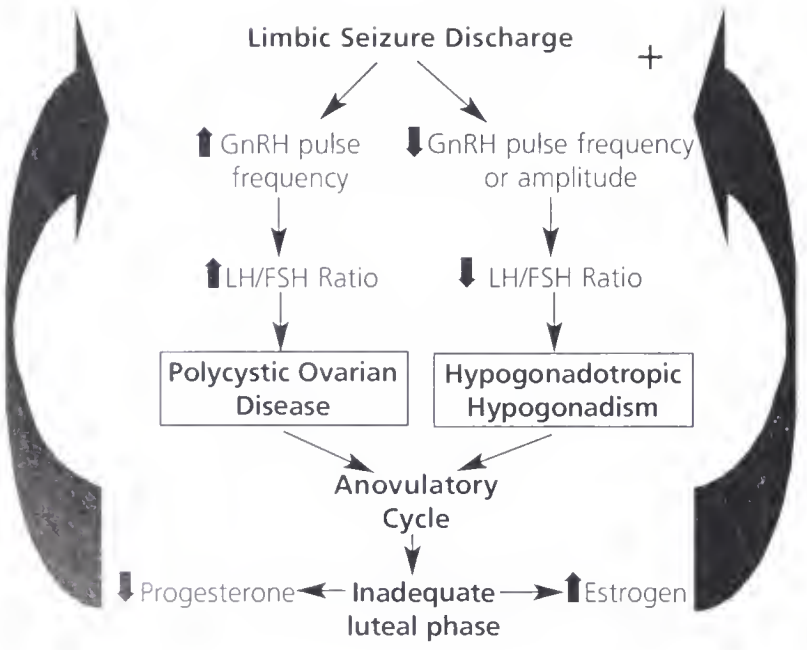

Figure 2. *A potential mechanism of action between limbic seizures and reproductive endocrine disorders. Alterations in GnRH pulse frequency and/or amplitude will differentially affect the biosynthesis of LH and FSH, such that the ratio of LH/FSH is altered. This may give rise to endocrine abnormalities that would, in turn, cause anovulatory cycles with inadequate luteal phases. The net effect is unopposed, high circulating estrogen – a hormone known to facilitate limbic seizure activity in rats – and low circulating progesterone – a hormone known to suppress limbic seizure activity[68]. GnRH, gonadotropin releasing hormone; LH, luteinizing hormone; FSH, follicle stimulating hormone.*

Electroshock Seizures

In addition to limbic seizures, primary generalized seizures also appear to cause reproductive dysfunction in rats. Repeated electroconvulsive shocks delay the onset of puberty and the initiation of ovarian cyclicity in juvenile female rats.[68,69] In adult, ovariectomized female rats primed with estrogen, electroshock treatment attenuates the positive feedback effect of progesterone on LH and FSH.[44,69] This suggests that electroshock seizures modify the hypothalamic-pituitary-axis in female rats by attenuating its responsiveness to gonadal steroid feedback regulation.

In male rats, repeated maximal electroshock seizures cause a transient hypogonadal state (i.e., decreased serum testosterone and testis, epididymis and prostate weight) that recovers to normal within 6 wks of the last seizure.[61] The transient decrease in gonadal activity observed after repeated electroshock seizures could reflect activation of systems in the brain that inhibit GnRH release (i.e., GABAergic and opioid pathways[14]). This would result in reduced pituitary LH and FSH secretion. In support of this hypothesis, generalized seizures have been shown to increase the production of adrenocorticotropic hormone (ACTH) and ß-endorphin from the pituitary.[70] ß-endorphin is well known to suppress pulsatile GnRH release[71]; thereby providing one mechanism in which generalized seizures could cause hypogonadotropic hypogonadism.

While hypogonadal function was only transient after electroshock treatment in male rats, there was a long-term elevation in serum prolactin, estrogen and pituitary weight 6 wks after the last electroshock seizure.[61] This suggests that repeated electroshock seizures progressively alter the neuroendocrine regulation of prolactin secretion. This result is consistent with clinical observations that electroconvulsive therapy causes elevations in serum prolactin in both depressed and schizophrenic patients.[72,73]

Why electroshock seizures give rise to transient hypogonadism while limbic-kindled seizures give rise to hypergonadism in male rats is unclear. It may be that focal limbic seizures and generalized seizures utilize different regulatory pathways that project to and differentially modify the pulsatile release of hypothalamic GnRH.[6,28] For example, kindled seizures may stimulate gonadotropin release which promotes hypergonadal function, while electroshock seizures may decrease gonadotropin secretion, producing transient hypogonadism. Such comparisons, however, would be premature in view of the considerable differences between the two experimental paradigms, in terms of both the number of stimuli applied, the intervals between stimuli and the total number of seizures experienced by each animal.

Do Changes in Reproductive Function Alter Seizure Susceptibility?

High affinity receptors for sex steroids have been identified in many regions of limbie struetures, including the amygdala and hippocampus.[74,75] Estrogen and androgen receptors are highly coneentrated in the amygdala, while progesterone and mineraloeortieoid receptors are highly loealized in the hippoeampus.[74-77] Studies in our lab have shown that estrogen lowers limbie seizure thresholds and enhances seizure activity, while progesterone raises limbie seizure thresholds and depresses seizure development.[78,79] The effect of limbie seizures on eireulating gonadal hormone levels is therefore important not only from the perspective of the information it provides regarding seizure-induced changes in reproduetive funetion, but also beeause these changes may themselves eontribute to the responses of the brain to eleetrieal stimulation. This provides another level of interaetion between limbie struetures and the hypothalamie-pituitary-gonadal axis.

In epileptie females, seizure induced alterations in menstrual eyclieity might potentiate or suppress seizure oeeurrenee. Epileptie patients with anovulatory eyeles (i.e., ~25% of epileptie patients[5,40]) are exposed to ehronie unopposed estrogen, sinee in the absence of an ovulatory surge of gonadotropins, the ovary fails to form funetional eorpora lutea. The result is a failure of progesterone levels to rise during the luteal phase (i.e., inadequate luteal phase). As mentioned earlier, unopposed estrogen is proeonvulsive and tends to heighten interietal epileptiform activity.[78-80] In eontrast, women experieneing amenorrhea – as a result of limbie seizure "overstimulation of hypothalamie GnRH secretion[19-21]" – may be protected against seizures. This would be due to the laek of ovarian steroid produetion and laek of estrogen potentiation of neural activity.

In epileptic males, limbic seizures might eontribute to the development of hypergonadism, since sueh an effect was observed in male rats.[61] Hypergonadal funetion is eharaeterized by inereased serum levels of testosterone - which have been shown to lower seizure thresholds in limbie structures and enhanee seizure development in male rodents.[79] Thus, seizure indueed ehanges in gonadal funetion eould in turn potential seizure activity.

In stark contrast to limbie seizures, studies in male rodents imply that patients with intraetable epilepsy who experienee frequent generalized seizures and/or patients reeeiving repeated electroshock therapy for treatment of depression may experience temporary hypogonadism and henee, reduced spermatogenesis and libido. Since testosterone potentiates seizure activity in the brain, decreased serum testosterone levels as a eonsequenee of hypogonadal funetion would be expeeted to deerease seizure susceptibility – at least in the short term.

Conclusions

Observations in animals are consistent with the hypothesis that reproductive dysfunetion in patients with epilepsy – in partieular temporal lobe epilepsy – might reflect seizure-indueed ehanges in the neuroendocrine regulation of gonadal funetion. In female rodents, both ehemieal and electrically-induced seizures disrupt normal ovarian eyelieity.[44-46] Amygdala kindled seizures also cause the development of polyeystic ovaries and premature reproductive aging of the hypothalamic-pituitary neuroendoerine axis.[54] At the level of the ovary, follieles fail to rupture and eorpora lutea do not develop, resulting in ehronie estrogen exposure.[54] Unopposed estrogen is known to enhanee seizure suseeptibility.[78] In male rodents, limbic-kindled seizures and generalized electroshock seizures differentially affeet reproductive function. Amygdala kindled seizures tend to increase some parameters of reproduetive funetion sueh as serum androgen levels and testis and epididymis weight.[61] In contrast, repeated eleetroshoek seizures induee a transient reduetion in testieular androgen production, with a coneomitant regression in male aceessory reproductive struetures.[61]

If the analogy to the rat is correct, the differenees in levels and patterns of reproductive endoerine seeretion may relate to the eharaeteristics of the epilepsy, including elassifieation and nature of paroxysmal diseharges. Through a better understanding of the mechanisms responsible for seizure-indueed alterations in reproduetive funetion, it may be possible to design improved therapeutie approaehes to the management of women and men with epilepsy, as well as epileptie ehildren as they approaeh puberty, while simultaneously optimizing eontrol over seizure activity.

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References

1. Webber MP, Hauser WA, Ottman R, and Annegers JF. (1986). Fertility in persons with epilepsy. *Epilepsia.* 27: 746-52.
2. Morrell MJ. (1991). Sexual dysfunction in epilepsy. *Epilepsia.* 32: S38-46.
3. Morrell MJ, Sperling MR, Stecker M, and Dichter MA. (1994). Sexual dysfunction in partial epilepsy: A deficit in physiological sexual arousal. *Neurology.* 44: 243-47.
4. Cramer JA and Jones EE. (1991). Reproductive function in epilepsy. *Epilepsia.* 32: S19-26.
5. Cummings LN, Giudice L, and Morrell MJ. (1995). Ovulatory Function in Epilepsy. *Epilepsia.* 36: 355-359.
6. Herzog AG. (1989). A hypothesis to integrate partial seizures of temporal lobe origin and reproductive disorders. *Epilepsy Res.* 3: 151-159.
7. Isojarvi JI, Laatikainen TJ, Pakarinen AJ, *et al.* (1993). Polycystic ovaries

[illegible] in women taking valproate for epilepsy. *N Eng J* [illegible] 1383-1388.

5. [illegible]r GT and Morrell MJ. (1996). Nocturnal penile tumescence and [illegible] evaluation in men with epilepsy. *Epilepsia*. 37: 1211-1214.
6. Herzog AG, Seibel MM, Schomer DL, *et al.* (1986). Reproductive endocrine disorders in men with partial seizures of temporal lobe origin. *Arch Neurology*. 43: 341-346.
10. Shukla GD, Srivastabe OM, and Katiuan BC. (1979). Sexual disturbances in temporal lobe epilepsy: a controlled study. *Brain J Psychiatry*. 134: 288-292.
11. Taneja N, Kucheria K, Jain S, and Maheshware MC. (1994). Effect of phenytoin on semen. *Epilepsia*. 35: 136-140.
12. Schupf N and Ottman R. (1994). Likelihood of pregnancy in individuals with idiopathic/cryptogenic epilepsy: Social and biologic influences. *Epilepsia*. 35: 750-756.
13. Herzog AG. (1997). *Epilepsy: A comprehensive textbook*. Engel J and Pedley TA (eds). Lippincott Raven Publishers: Philadelphia, pp. 2013-2019.
14. Knobil E and Hotchkiss J. (1988). *The Physiology of Reproduction*. Knobil E and Neil J (eds). Raven Press: New York, pp. 1971-1994.
15. Meo R, Bilo L, Nappi C, *et al.* (1993). Derangement of the hypothalamic GnRH pulse generator in women with epilepsy. *Seizure*. 2: 241-252.
16. Bilo L, Meo R, Valentino R *et al.* (1991). Abnormal pattern of luteinizing hormone pusatility in women with epilepsy. *Fertil Steril*. 55: 705-711.
17. Dana Haeri J, Trimble MR, and Oxley J. (1983). Prolactin and gonadotrophin changes following generalised and partual seizures. *J Neurol Neurosurg Psychiatry*. 46: 331-335.
18. Mechain C, Cedrin I, Pandian C, and Lemay A. (1933). Serum FSH bioactivity and response to acute gonadotrophin releasing hormone GnRH) agonist stimulation in patients with polycystic ovary syndrome (PCOS) as compared to control groups. *Clin Endocrinol*. 38: 311-320.
19. Herzog AG, Russell V, Vaitukaitis JL, *et al.* (1982). Neuroendocrine dysfunction in temporal lobe epilepsy. *Arch Neurol*. 39: 133-135.
20. Spark RF, Wills CA, and Royal H. (1984). Hypogonadism, hyperprolactinemia and temporal lobe epilepsy in hyposexual men. *Lancet*. 1: 413-417.
21. Bauer J, Wildt L, Flugel D, and Stefan H. (1992). The effect of a synthetic GnRH analogue on catamenial epilepsy: a study in ten patients. *J Neurol*. 239: 284-286.
22. Velasco ME and Taleisnik S. (1971). Effects of the interruption of amygdaloid and hippocampal afferents to the medial hypothalamus on gonadotropin release. *J Endocrinology*. 51: 41-55.
23. Zolovick AJ. (1972). *The Neurobiology of the Amygdaa*. Eleftheriou BE (ed). Plenum Press: New York, pp. 643-83.
24. Martin JB, Reichlin S, and Brown GM. (1977). *Clinical Neuroendocrinology*. Davis FA (ed.). Lippincott-Raven Publishers: Philadelphia, pp. 129-145.
25. Gloor P. (1975). Complex partial seizures and their treatment. *In: Advances in Epilepsy, Vol II. Physiology of the limbic system*. Penry JK and Daly DD (eds). Raven Press: New York, pp. 27-35.
26. Sawyer CH. (1972). *The Neurobiology of the Amygdala*. Eleftheriou BE (ed). Plenum Press: New York, pp. 745-762.
27. Herzog AG, Drislane FW, Schomer DL, *et al.* (1990). Abnormal pulsatile secretion of luteinizing hormone in men with epilepsy: relationship to laterality and nature of paroxysmal discharges. *Neurology*. 40: 1557-1561.
28. Herzog AG. (1993). A relationship between particular reproductive endocrine disorders and the laterality of epileptiform discharges in women with epilepsy. *Neurology*. 43: 1907-1910.
29. Adamec RE and Stark-Adamec C. (1985). Limbic traces and interictal behaviour: basic science and clinical approaches. *Int J Neurol*. 19-20: 117-26.
30. Schachter SC. (1988). Hormonal considerations in women with seizures. *Arch Neurol*. 45: 1267-1270.
31. Beastall GH, Cowan RA, Gray JM, and Fogelman I. (1985). Hormone binding globulins and anticonvulsant therapy. *Scott Med J*. 30: 101-105.
32. Perrucca E. (1987). Clinical implications of hepatic microsomal enzyme induction by antiepileptic drugs. *Pharmacol Ther*. 33: 139-44.
33. Morrell MJ. (1992). Hormones and epilepsy through the lifetime. *Epilepsia*. 33: S49-S61.
34. Back DJ, Bates M, Bowden A, *et al.* (1980). The interaction of phenobarbital and other anticonvulsants with oral contraceptive steroid therapy. *Contraception*. 22: 495-503.
35. Coulam CB and Annegers JF. (1979). Do oral anticonvulsants reduce the efficacy of oral contraceptives? *Epilepsia*. 20: 519-26.
36. Gallagher BB, Flanigin HF, King DW, and Littleton WH. (1987). The effect of electrical stimulation of medial temporal lobe structures in epileptic patients upon ACTH, prolactin, and growth hormone. *Neurology*. 37: 290-303.
37. Jones TH. (1991). Sodium valproate-induced menstrual disturbance in young women. *Horm Res*. 35: 82-85.
38. Isojarvi JIT, Pakarinen AJ, Ylipalosarri PJ, and Mullyla VV. (1990). Serum hormones in male epileptic patients receiving anticonvulsant medication. *Arch Neurol*. 47: 670-676.
39. Macphee FJA, Larkin JG, Butler E, *et al.* (1988). Circulating hormones and pituitary responsiveness in young epileptic men receiving long-term antiepileptic medication. *Epilepsia*. 29: 468-475.
40. Mattson RH and Cramer JA. (1985). Epilepsy, sex hormones, and antiepileptic drugs. *Epilepsia*. 26: S40-S51.
41. Kuhn-Velten WM, Herzog AG, and Muller MR. (1990). Acute effects of anticonvulsant drugs on gonadotropin-stimulated and precursor-supported testicular androgen production. *Eur J Pharmacol*. 181: 151-155.
42. Isojarvi JIT, Laatikainen TJ, Knip M, *et al.* (1996). Obesity and endocrine disorders in women taking valproate for epilepsy. *Ann Neurol*. 39: 579-584.
43. Herzog AG, Seibel MM, Schomer DL, *et al.* (1986). Reproductive endocrine disorders in women with partial seizures of temporal lobe origin. *Arch Neurol*. 43: 341-346.
44. Bhanot R and Wilkinson M. (1983). Repeated convulsions induce pseudopregnancy in the intact rat and inhibit steroid-mediated gonadotrophin secretion in the ovariectomized rat. *J Endocrinol*. 95: 43-48.
45. Amado D, Verreschi IT, Berzaghi MP, and Cavalheiro EA. (1987). Effects of intrahippocampal injection of kainic acid on estrous cycle in rats. *Braz J Med Biol Res*. 20: 829-832.
46. Amado D and Cavalheiro EA. (1998). Hormonal and gestational parameters in female rats submitted to the pilocarpine model of epilepsy. *Epilepsy Res*. 32: 266-274.
47. Kling A, Orback J, Schwartz NB, and Towne JC. (1960). Injury to the limbic system and associated structures in cats. *Arch Gen Psychiatry*. 3: 391-419.
48. Yamada T and Greer MA. (1960). The effect of bilateral ablation of the amygdala on endocrine function in the rat. *Endocrinology*. 66: 565-674.
49. Erickson LB and Wada A. (1970). Effect of lesions in the temporal lobe and rhinencephalon on reproductive function in adult female rhesus monkeys. *Fertil Steril*. 21: 434-54.
50. Kluver H and Bucy P. (1939). Preliminary analysis of functions of the temporal lobes in monkeys. *Arch Neurol Psychiatry*. 42: 979-1000.
51. Wood CD. (1958). Behavioral changes following discrete lesions of temporal lobe structures. *Neurology*. 8: 215-220.
52. Kulkarni SK and George B. (1994). Kindling model of epilepsy. *Meth Find Exp Clin Pharmacol*. 16: 735-745.
53. Sato M, Racine RJ, and McIntyre DC. (1990). Kindling: basic mechanisms and clinical validity. *Electroenceph Clin Neurophysiol*. 76: 459-472.
54. Edwards HE, Burnham WM, Ng MM, and MacLusky NJ. (1999a). Limbic seizures alter reproductive function in the female rat. *Epilepsy Res*. 40: 1370-1377.
55. Brawer JR, Schipper H, and Naftolin F. (1980). Ovary-dependent degeneration of hypothalamic arcuate nucleus. *Endocrinology*. 107: 274-281.
56. Brawer JR and Sonnenschein C. (1976). Cytopathological effects of estradiol on the arcuate nucleus of the female rat: A possible mechanism for pituitary tumorigenesis. *Am J Anat*. 144: 57-64.
57. Yen SSC, Vela P, and Rankin J. (1970). Inappropriate secretion of follicle stimulating hormone and luteinizing hormone in polycystic ovarian disease. *J Clin Endocrino Metab*. 30: 435-442.
58. Finch CE. (1979). Neuroendocrine mechanisms and aging. *Fed Proc*. 38: 178-183.
59. Weiland NG and Wise PM. (1990). Aging progressively decreases the den-

sities and alters the diurnal rhythms of alpha 1-adrenergic receptors in selected hypothalamic regions. *Endocrinol.* 126: 2392-2397.

60. Simard M, Brawer JR, and Farookhi R. (1987). An intractable, ovary-independent impairment in hypothalamo-pituitary function in the estradiol-valerate-induced polycystic ovarian condition in the rat. *Biol Reprod.* 36:1229-1237.
61. Edwards HE, Burnham WM, and MacLusky NJ. (1999b). Focal and generalized seizures differentially affect reproductive physiology in the male rat. *Epilepsy Res.* 40:1490-148.
62. Lieberman ME, Maurer RA, Claude P, *et al.* (1981). Regulation of pituitary growth and prolactin gene expression by estrogen. *Adv Exp Med Biol.* 128:151-163.
63. Dreifuss JJ, Murphy JT, and Gloor P. (1986). Contrasting effects of two identified amygdaloid efferent pathways on single hypothalamic neurons. *J Neurophysiology.* 31: 237-248.
64. Renaud LP. (1976). Influence of amygdala stimulation on the activity of identified tuberinfundibular neurons in the rat hypothalamus. *J Physiol.* 260: 237-252.
65. Finkel DM, Phillips JL, and Snyder PJ. (1985). Stimulation of spermatogenesis by gonadotropins in men with hypogonadotropic hypogonadism. *N Engl J Med.* 313: 651-655.
66. Spiteri J and Nieschlag E. (1993). Paracrine factors relevant to the regulation of spermatogenesis - a review. *J Reprod Fertil.* 98: 1-14.
67. Swerdloff RS, Wang C, and Bhasin S. (1992). Developments in the control of testicular function. Bailliere *Clin Endocrinol Metab.* 6: 451-483.
68. Carson RC and Wilkinson M. (1989). Seizure-induced delay of puberty in female rats: effects of age, stress and opioid antagonists. *J Endocrinol.* 121: 229-238.
69. Bhanot R and Wilkinson M. (1984). Differential effects of flurothyl- and electro-convulsive shock on sexual maturation and prolactin release in the rat. *Exp Brain Res.* 5:32-39.
70. Pritchard PB. (1991). The effect of seizures on hormones. *Epilepsia.* 32: S46-S50
71. Faletti AG, Mastronardi CA, Lomniczi A, *et al.* (1999). Beta-Endorphin blocks luteinizing hormone-releasing hormone release by inhibiting the nitricoxidergic pathway controlling its release. *Proc Natl Acad Sci U S A.* 96:1722-1726.
72. Meco G, Casacchia M, Carchedi F, *et al.* (1978). Prolactin response to repeated electroconvulsive therapy in acute schizophrenia. *Lancet.* 2: 999-1012.
73. O'Dea JPK, Gould D, Hallberg M, and Wieland RG. (1978). Prolactin changes during electroconvulsive therapy. *Am J Psychiatry.* 135: 609-611.
74. Chao HM, Choo PH, and McEwen BS. (1989). Glucocorticoid and mineralocorticoid receptor mRNA expression in rat brain. *Neuroendocrinology.* 50: 365-371.
75. Simerly RB, Chang C, Muramatsu M, and Swanson LW. (1990). Distribution of androgen and estrogen receptor mRNA-containing cells in the rat brain: an in situ hybridization study. *J Comp Neurol.* 294: 76-95.
76. Sar M, Lubahn D, French TS, and Wilson EM. (1990). Immunohistochemical localization of the androgen receptor in rat and human tissues. *Endocrinology.* 127: 3180-3186.
77. Shughrue PJ, Lane MV, and Merchenthaler I. (1997). Comparative distribution of estrogen receptor-ß and -ß mRNA in the rat central nervous system. *J Comp Neurol.* 388: 507-525.
78. Edwards HE, Burnham WM, Mendonca A, *et al.* (1999c). Steroid hormones affect afterdischarge thresholds and kindling rates in the limbic system in adult female rats. *Brain Research.* 838:136-150.
79. Edwards HE, Burnham WM, and MacLusky NJ. (1999d). Testosterone and its metabolites affect afterdischarge thresholds and the development of amygdala kindled seizures in male rats. *Brain Research.* 838:151-157.
80. Herzog AG. (1991). Reproductive endocrine considerations and hormonal therapy in men with epilepsy. *Epilepsia.* 6:S27-S33.

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The Physiological Roles of Cadherin Mediated Cell Adhesion

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Abstract

Cadherins are a family of cell adhesion molecules (CAMs) that mediate calcium dependent cell-cell interactions. These cellular interactions promote the formation of intercellular junctions, the establishment of cell polarity, and cell sorting during development, ultimately affecting the formation of tissues and the maintenance of tissue architecture. Additionally, cadherin mediated adhesion is involved in the regulation of cellular growth and differentiation, as well as apoptosis. However, the aberrant expression of cadherins may contribute to tumour progression. Thus, the precise regulation of cadherin expression is needed to ensure their proper functions. This paper reviews the structure and regulation of cadherins, as well as the physiological roles served by cadherin mediated adhesion.

Introduction

Cadherins encompass a family of structurally related cell adhesion molecules (CAMs) that mediate calcium dependent cell-cell homotypic adhesion in vertebrates and invertebrates (reviewed in 1-7). The cadherin superfamily is divided into several families according to the number of extracellular (EC) domains tandemly repeated in the extracellular segments of cadherins.[5] The type I (also referred to as classical) cadherins are the most extensively studied and comprise E-cadherin, N-cadherin, and P-cadherin. E-cadherin is expressed mainly in epithelial tissues, while N-cadherin and P-cadherin are expressed mainly in neural and placental tissues, respectively. Other members of the cadherin superfamily include the type II classic cadherins, desmosomal cadherins, protocadherins, and other more distantly related cadherins.[1] This paper will focus on the structure and regulation of the classical cadherins, as well as the signalling pathways implicated in cadherin mediated adhesion. The function of cadherins will be reviewed in the context of tumour progression, cell survival, and immune regulation.

Structure of the Classical Cadherins and the Cadherin-Catenin Complex

The classical cadherins are synthesized as precursor molecules with an approximate molecular weight of 135 kDa. Following glycosylation, phosphorylation, and proteolytic cleavage, a mature cadherin protein with a molecular weight of 120 kDa is produced.[8-11] Each member contains five EC domains (each containing approximately 110 amino acids), a single transmembrane domain, and two cytoplasmic domains (as shown in Figure 1).[12-24]

The tripeptide histidine-alanine-valine (HAV), found in the first EC domain,[15] is the cell adhesion recognition (CAR) sequence of cadherins responsible for homotypic binding. It is now known that histidine and valine form the adhesive interface and alanine is recessed in the hydrophobic core fragment of the CAR sequence.[16] Antibodies and synthetic peptides directed against the CAR sequence block cadherin mediated adhesion and function. Residues flanking the HAV sequence are believed to play a role in binding specificity. The binding specificities of P- and E-cadherins are interchanged in recombinant chimeric proteins generated by switching their amino-terminal EC domains.[17] The roles of the four other EC repeats have yet to be elucidated but it is believed that they may simply act as

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spacers in order to project the receptor to a necessary distance from the cell membrane.[18] The five EC repeats form four calcium binding pockets, each between two successive repeats.[19-20] The acidic amino acid motifs DXNDN and DXD are conserved motifs capable of binding calcium.[21] The binding of calcium is necessary for cadherin function and confers protection from proteases.[22] The role of calcium is likely to form and maintain the active conformation of the classical cadherins.[23]

The cytoplasmic domain (CD) is highly conserved and interacts with several proteins collectively known as the catenins, which link cadherins to the cytoskeleton (Figure 1).[24-26] The formation of the cadherin-catenin complex is required for stable cell adhesion.[24-26] Studies employing deletion mutagenesis of the cytoplasmic domain of E-cadherin have localized the catenin binding domain to a 30 amino acid region containing a series of phosphorylated serine residues.[14] Deletion of the cytoplasmic tail or of the catenin binding site abrogates cadherin mediated aggregation of cultured cells.[14,25,27]

The catenin family is comprised of several members, including α-catenin, ß-catenin, γ-catenin, and p120^{ctn} (reviewed in 28, 29). ß-catenin and γ-catenin (plakoglobin) bind in a mutually exclusive manner to the conserved catenin-binding domain (Figure 1). α-catenin then links either the ß- or γ-catenin-cadherin complex to actin, either directly, or indirectly via α-actinin.[30] Protein tyrosine phosphatases interact directly with the cytoplasmic region of N-cadherin, regulating tyrosine phosphorylation events of ß-catenin, and in turn, modulating cadherin function.[31,32] Agents which inhibit the activity of the phosphatase lead to an accumulation of tyrosine phosphate on ß-catenin, which will therefore uncouple N-cadherin from the cytoskeleton, subsequently leading to a loss of cadherin function. Recently, it has been shown that the non-receptor protein tyrosine phosphatase PTP1B is a candidate N-cadherin associated phosphatase.[32]

Despite the high degree of homology between γ-catenin and ß-catenin, the physiological role of γ-catenin is unclear. γ-catenin is a major component of desmosomes and is capable of interacting with desmosomal cadherins.[33] ß-catenin knock out mice show a deficiency in adhesion indicating that γ-catenin cannot substitute for ß-catenin.[34]

p120^{ctn} was initially defined as a substrate for the oncogenic tyrosine kinase *src* and growth factor receptor tyrosine kinases.[35] However, p120^{ctn} lacks structural motifs such as the SH2 and SH3 domains normally found in tyrosine kinase receptors. p120^{ctn} associates with the carboxyl terminal tail of cadherins in the juxtamembrane region close to the ß/γ-catenin binding

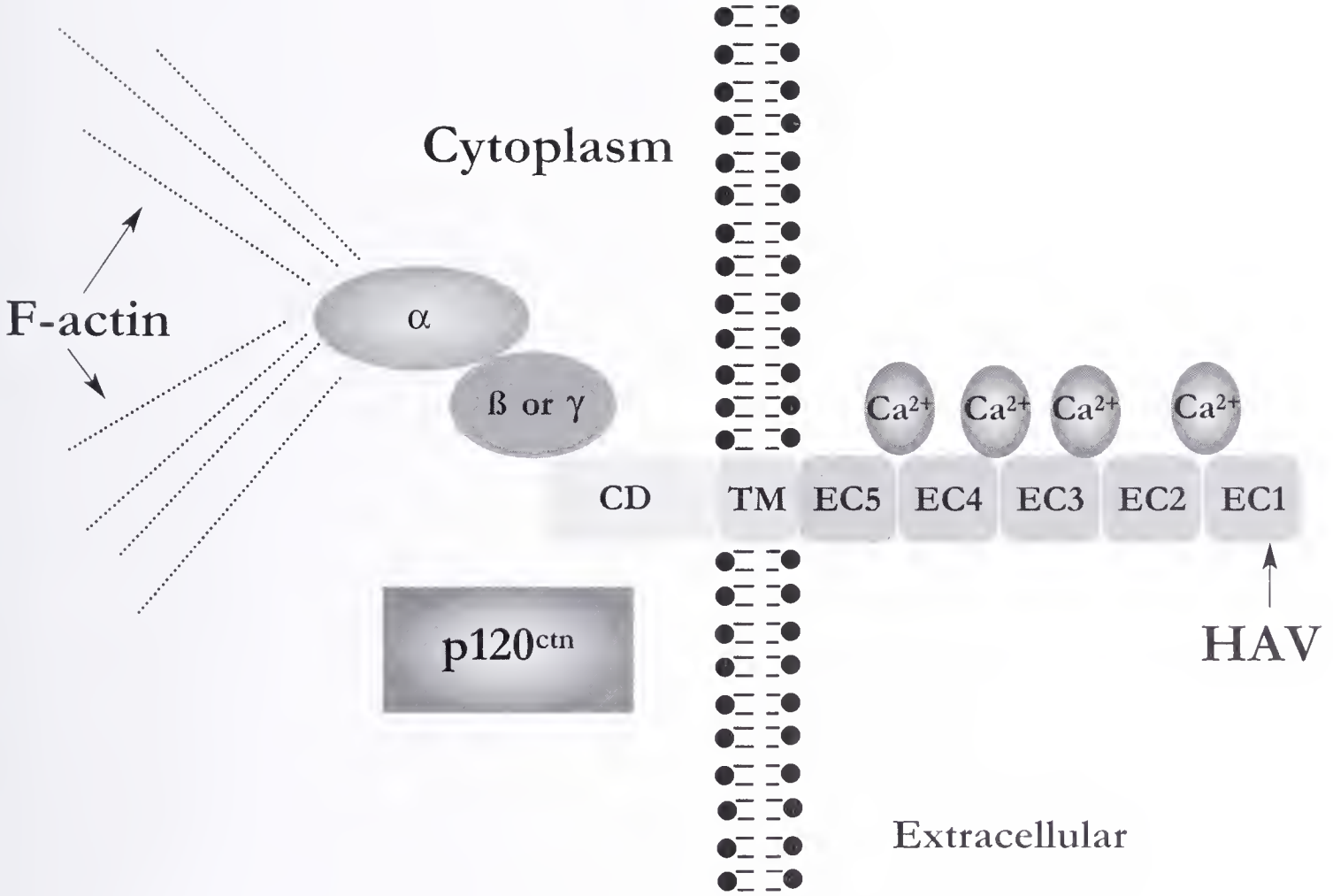

Figure 1. *Structure of the cadherin-catenin complex.*

domain.[37] The role of p120^{ctn} is not exactly known, although authors have speculated a role in cadherin dimerization,[38] and others have suggested that tyrosine phosphorylation of p120^{ctn} induces its dissociation from cadherin-catenin complexes, allowing it to interact with other effector molecules.[39]

The Role of Cadherin Clustering in Cell-Cell Adhesion

Recent observations support cadherin dimerization or clustering, as a means of enhancing cell adhesion.[26,38,40] It was initially shown by Brieher *et al.* that a C-cadherin ectodomain existed as a stable dimer, and that the dimeric forms were necessary to induce the aggregation of substrates coated with C-cadherin.[26] Yap *et al.* constructed a chimeric protein in which the cytoplasmic tail of C-cadherin was replaced by three tandem repeats of FKBP modules. The addition of FK-1012, which concurrently binds to FKBP domains on separate cadherin molecules, induced dimerization, leading to a substantial increase in adhesion.[41] E-cadherin homophilic adhesion requires the formation of parallel *cis* dimers (on the same surface) for the formation of antiparallel *trans* dimers (cell to cell).[41] It is postulated that *cis* interaction may initiate a change in conformation and allow effective adhesion to occur.[41] The two subunits of the lateral dimers of E-cadherin are joined at the calcium binding site between EC1 and EC2.[19] Calcium mediates this interaction indirectly. Analysis of the crystal structure of the EC1 domain of N-cadherin also indicates that a stable, parallel, lateral dimer is a prerequisite for homophilic binding activity.[16] However, in this model, lateral dimers are formed via a hydrophobic interaction, in which a tryptophan of one subunit of the lateral dimer integrates into the hydrophobic pocket of the other subunit.[16] While it is clear that lateral dimerization plays a significant role in cadherin mediated homophilic adhesion, the exact mechanism by which this occurs is unknown. The strengthening of the adhesion could be mediated simply by the increased avidity of the dimeric form or, alternatively, *cis* dimerization may be a key regulatory step to the production of an active conformation. Finally, Shapiro *et al.* have suggested that lateral cadherin dimers projecting from the two cell surfaces could interdigitate to form a continuous linear supramolecular zipper.[18]

p120^{ctn} has been implicated in cadherin clustering. Cells expressing cadherins lacking the putative p120^{ctn} binding site were not able to dimerize.[38] It is speculated that a homodimer cadherin p120^{ctn} complex may be necessary to increase the rates of initial homotypic recognition and subsequent binding between cadherin molecules on two adhering cells. Subsequently, α-catenin, ß-catenin and the actin skeleton may stabilize the complex and allow for a strengthening of cell-cell adhesion.

Cadherin-Catenin Signal Transduction

The role of cadherins has traditionally been associated with cell-cell adhesion and the maintenance of tissue architecture. There is emerging evidence that cadherins may mediate signalling events that influence gene transcription and ultimately affect cell growth and differentiation. In a recent study, homophilic cell-cell adhesion was mimicked by the use of Madin-Darby canine kidney (MDCK) cells and human breast MCF10A cells incubated with immobilized E-cadherin antibodies. This led to an increase of tyrosine phosphorylated proteins with molecular weights of 120, 130, and 180 kDa, one of which was identified as a ras-GTPase activating protein (GAP).[42] Since actin recruitment to cadherin-based junctions requires Rac and Rho activity, it is possible that cadherin signalling may activate ras-GAP, which may in turn activate Rac and Rho, leading to the formation of stable adherens junctions.[29,43] In addition, N-cadherin-mediated binding results in increased cadherin and ß-catenin levels in adherens junctions, as well as an increased level of tyrosine phosphorylated proteins in cell-cell junctions.[44]

Cytoplasmic ß-catenin interacts with other proteins and is an integral part of the Wnt signalling pathway in vertebrates (reviewed in 45, 46). Wnt proteins are secreted glycoproteins implicated in the regulation of cell fate decisions during vertebrate formation. Wnt proteins interact with transmembrane receptors of the Frizzled (Fz) family, activating Dishevelled (Dsh) proteins, which in turn, inhibit glycogen synthase kinase 3ß (GSK3ß). The inhibition of GSK3ß leads to the activation of ß-catenin, allowing for its accumulation[39,47] and association with transcription factors of the T cell factor (TCF) / lymphocyte enhancing factor (LEF-1) family.[48,49] This complex translocates to the nucleus and influences gene transcription. In the absence of a Wnt-1 ligand, ß-catenin complexes with the tumour suppressor adenomatous polyposis coli (APC) and is then degraded via ubiquitination and proteasome mediated proteolysis.[50] It has been shown that ß-catenin levels were enhanced in colon cancers[51,52] and melanomas[53] where mutations in APC existed. It has been suggested that the accumulation of ß-catenin results in the continuous activation of the Wnt signal transduction cascade, activating the transcription of genes associated with cell survival and proliferation.[54] Connexins,[55] homeobox genes,[56] and c-*myc*[57] are among the genes targeted by the Wnt pathway. There is also evidence of cross-talk between integrin-mediated and Wnt-mediated signalling pathways.[58] Integrin-linked kinase (ILK) is a serine/threonine kinase whose overexpression causes loss of cell-cell adhesion, translocation of ß-catenin and the activation of ß-catenin/LEF-1 dependent transcription.[58]

Classical Cadherin Expression and Its Implication in Tumour Invasiveness

The first cadherins identified by cDNA cloning were E-cadherin, N-cadherin, and P-cadherin (reviewed in 4, 6, 29). E-cadherin is expressed mainly in epithelial tissues, N-cadherin in neural tissues and striated muscle, and P-cadherin is limited to skin, placenta, and prostate. Table 1 summarizes the main characteristics of classical cadherins.

Cadherins are found mainly in adherens junctions, such as zonula adherens junctions, synaptic junctions, autotypic junc-

Table 1
Human classical cadherins. Modified from Potter *et al.*[29]

Name	Symbol	Locus	Main Expression	Molecular Weight
E-cadherin	CDH1	16q22.1	Epithelia	124kDa
N-cadherin	CDH2	18q11.2	Neuronal cells, skeletal muscle, and cardiac muscle	130 kDa
P-cadherin	CDH3	16q22.1	Skin, prostate, and placenta	118 kDa

tions in the myelin sheath, and the intercalated disks of cardiac myocytes (reviewed in 2, 4, 6). These junctions, in association with the actin skeleton, serve to bring about morphological transitions that underlie tissue formation and maintain tissue architecture in the adult organism. The distribution of cadherins during embryogenesis is tightly regulated, as the loss of cadherin expression or its ectopic expression can alter the phenotype of a cell, and disrupt cell differentiation. For example, cultured epiblast cells from primitive streak stage embryos exhibit a loss of E-cadherin concurrent with a gain in N-cadherin expression.[59] N-cadherin positive cells, in turn, continue to differentiate into skeletal and cardiac muscle. Antibodies blocking N-cadherin result in the arrest of muscle differentiation.[60] In a second example, melanocyte development from migrating neural crest cells requires the detachment of neural crest cells from the neural tube, which occurs only upon the downregulation of N-cadherin and the upregulation of cadherin-7 on neural crest cells.[61]

It has been shown that in some cases, cultured cells derived from oral squamous cell carcinomas expressing N-cadherin display an increase in cell motility and invasion, as compared to cultured cells derived from E-cadherin positive carcinomas.[62] It was suggested that E-cadherin mediates signal transduction events that would maintain an epithelial phenotype, while N-cadherin signalling instructs the cell to adopt a motile, fibroblastic-like phenotype. A number of studies have associated a reduced expression of E-cadherin with a wide range of carcinomas, including breast,[63-65] head and neck,[66,67] gastrointestinal,[68] thyroid,[69,70] and prostate.[71] In general, many of these studies have correlated the loss of E-cadherin-mediated adhesion with dedifferentiated tumours, increased tumour invasiveness, and poor clinical prognosis. Recently, germline mutations of the E-cadherin gene were shown to induce a familial form of gastric cancer.[72] However, E-cadherin expression has not been seen to be uniformly successful in reversing the invasiveness and malignancy of tumour cells,[73] suggesting that while the loss of E-cadherin may contribute to the invasive and metastatic potential of a malignancy, it is unlikely to be the sole determinant. In summary, cadherin expression must be tightly regulated during morphogenesis, as well as for the maintenance of tissue organization. Disturbances in this regulation may lead to tumour progression.

Cadherins and Apoptosis

The formation of E-cadherin mediated multicellular aggregates has been shown to provide resistance to apoptosis.[74-76] These studies showed that E-cadherin mediated protection from apoptosis was paralleled by an upregulation of the Bcl-2 oncogene,[74] activation of the tumour suppressor Retinoblastoma (Rb),[75] as well as the phosphatidyl inositol (PI) 3-Kinase dependent activation of Akt.[76] The PI 3-kinase/Akt cascade is a signalling cascade that is critical for promoting cell survival in response to stress or growth factor deprivation. Similarly, investigators have demonstrated that N-cadherin mediated adhesion inhibits apoptosis.[77-80] Rat granulosa cells that express N-cadherin exhibit an increased rate of apoptosis when cultured in the presence of N-cadherin disrupting antibodies or the synthetic blocking peptide N-Ac-CHAVC-NH2.[77] It is postulated that N-cadherin expression by these cells mediates homophilic-homotypic adhesion promoting cell aggregation, and thereby promoting cell survival.[77] Peluso *et al.* have shown that N-cadherin interacts with the fibroblast growth factor (FGF) receptor, promoting signal transduction events through the FGF receptor.[80] It is hypothesized that such signal transduction pathways prevent apoptosis via protein kinase C (PKC) dependent mechanisms and the maintenance of calcium homeostasis.[80] The initiation of apoptosis requires the activity of a number of proteases and endonucleases that are calcium dependent.[80] It is likely that the survival pathway initiated by N-cadherin facilitates the uptake of calcium into intracellular stores, thereby sequestering the calcium from proteolytic enzymes and endonucleases.[80]

The Role of Cadherins in the Immune System

Recent publications have addressed the possibility that cadherins may play a role in the immune system. E-cadherin is expressed by both thymocytes and stromal cells in the murine thymus.[81,82] The inhibition of homotypic E-cadherin interaction in the thymus inhibit epithelial organization and thymocyte development.[82] Murine epidermal γδ T-cells and T-cell lymphoma lines derived from patients with cutaneous T-cell lym-

plasm. express E-cadherin and can interact directly with keratinocytes *in vitro*.[83,84] E cadherin can mediate heterophilic cell-cell adhesion with the integrin, $\alpha_1 \beta_1$.[85-87] This heterotypic interaction has been demonstrated between T lymphocytes and epithelial cells,[83,86] and there is evidence that the $\alpha_E \beta_7$-E-cadherin interaction is important in the pathology of rheumatoid arthritis.[88] Finally, pro-inflammatory cytokines interleukin 1 (IL-1) and tumour necrosis factor alpha (TNF-α), as well as lipopolysaccharide (LPS), induced a decrease in E-cadherin mRNA, paralleled by diminished homotypic cell-cell adhesion in feral-skin derived dendritic cells.[89] Langerhans cells are a type of dendritic cell that reside in the stratified squamous epithelia and are responsible for antigen trapping. Upon antigen exposure, a subset of Langerhans cells will display an activated phenotype, including an enhanced antigen presenting capacity, and will subsequently migrate to the T-cell regions of the regional lymph nodes.[90] It is hypothesized that a down-regulation of E-cadherin may be the initial step in Langerhans cell mobilization from the epidermis to lymphoid tissue.[91] Collectively, these studies suggest that E-cadherin may play an important role in the localization of Langerhans cells and dendritic epidermal T-cells to the epidermis, of immature thymocytes to the epithelial thymic rudiment, and of malignant T-cells to the skin of patients with cutaneous T-cell lymphoma. Finally, E-cadherin is also expressed in the bone marrow and mediates cell-cell interaction between the bone marrow stromal cells and hematopoietic cells during differentiation.[92]

N-cadherin is another potentially important cell adhesion molecule in the regulation of the immune system. N-cadherin is expressed by the leukemic T-cell line Jurkat[93,94] and it has been suggested that its expression may provide lymphoma T-cells with the ability to invade and metastasize into the mesenchymal tissue in the central nervous system,[95] a property that has long been noted in lymphoma cells. Furthermore, N-cadherin expression is regulated by ß1 and ß3 integrins,[96] cell adhesion molecules that are expressed by lymphocytes. It is possible that N-cadherin plays a role during lymphocyte recirculation and immune surveillance, or during lymphocyte development.

Summary

In recent years, we have come to realize that the role of cadherins in cell-cell adhesion is more complex than previously believed. Cadherin mediated adhesion is not only critical to the preservation of tissue integrity but may initiate signal transduction cascades that regulate the growth and differentiation of cells. This may occur directly, or via the Wnt pathway, mediated by ß-catenin. In addition, cadherins may facilitate close cell-cell contact thereby allowing other potential receptors and ligands to interact and generate signals that modulate cell growth and survival. Regardless of the precise mechanism, it is implicit that tight regulation of cadherin expression is needed, as a loss or gain of cadherin expression may alter the cellular phenotype, and adversely modulate embryogenesis and cell differentiation. Inappropriate expression of cadherin molecules has been proposed to be involved in various pathological mechanisms, from the protection of cell death and the dissemination of malignancy, to immune mediated disease processes. Identification of the specific molecular pathways triggered by cadherin mediated adhesion would allow us to better understand the physiological role of cadherins, as well as the potential pathophysiological consequences of cadherin dysregulation.

References

1. Suzuki ST. (1996). Structural and functional diversity of cadherin superfamily: Are new members of cadherin superfamily involved in signal transduction pathway? *J Cell Biochem.* 61:531-542.
2. Yap AS, Brieher WM, and Gumbiner BM. (1997). Molecular and functional analysis of cadherin-based adherens junctions. *Annu Rev Cell Dev Biol.* 13:119-46.
3. Yap AS. (1998). The morphogenetic role of cadherin cell adhesion molecules in human cancer: a thematic review. *Cancer Invest.* 16:252-261.
4. Takeichi M. (1991). Cadherin cell adhesion receptors as morphogenetic regulators. *Science.* 251:1451-1455.
5. Takeichi M. (1995). Morphogenetic roles of classic cadherins. *Curr Opin Cell Biol.* 7:619-627.
6. Munro S and Blaschuk O. (1996). The structure, function and regulation of cadherins. *In: Cell Adhesion and Invasion in Cancer Metastasis.* R. G. L. Company: Austin, pp. 17-34.
7. Knudsen KA, Frankowski C, Johnson KR, and Wheelock MJ. (1998). A role for cadherins in cellular signaling and differentiation. *J Cell Biochem Suppl.* 30-31:168-76.
8. Ringwald M, Schuh R,Vestweber D, *et al.* (1987). The structure of cell adhesion molecule uvomorulin. Insights into the molecular mechanism of calcium dependent cell adhesion. *EMBO J.* 6:3647-3653.
9. Ozawa M and Kemler R. (1990). Correct proteolytic cleavage is required for the adhesive function of uvomorulin. *J Cell Biol.* 111:1645-1650.
10. Shore EM and Nelson WJ. (1991). Biosynthesis of the cell adhesion molecule uvomorulin (E-cadherin) in Madin-Darby canine kidney epithelial cells. *J Biol Chem.* 266:19672-19680.
11. Stappert J and R. Kemler. (1994). A short core region of E-cadherin is essential for catenin binding and is highly phosphorylated. *Cell Adhes Commun.* 2:319-327.
12. Nagafuchi A, Shirayoshi Y, Okasaki K, *et al.* (1987). Transformation of cell adhesion properties by exogenously introduced E-cadherin cDNA. *Nature.* 329:341-343.
13. Ringwald M, Baribault H, Schimdt C, and Kemler R. (1991). The structure of the gene encoding for the mouse cell adhesion molecule uvomorulin. *Nucleic Acids Res.* 19:6533-6539.
14. Rimm D and Morrow J. (1994). Molecular cloning of human E-cadherin suggests a novel subdivision of the cadherin superfamily. *Biochem biophys Res Commun.* 200:1754-1761.
15. Blaschuk O, Sullivan R, David S, and Pouliot Y. (1990). Identification of a cadherin cell adhesion recognition sequence. *Dev Biol.* 139:227-229.
16. Shapiro L, Fannon AM, Kwong PD, *et al.* (1995). Structural basis of cell-cell adhesion by cadherins. *Nature.* 374:327-337.
17. Nose A, Tsuji K, and Takeichi M. (1990). Localization of specificity determining sites in cadherin cell adhesion molecules. *Cell.* 61:147-155.
18. Shapiro L, and Colman DR. (1998). Structural biology of cadherins in the nervous system. *Curr Opin Neurobiol.* 8:593-599.
19. Nagar B, Overduin M, Ikura M, and Rini JM. (1996). Structural basis of calcium-induced E-cadherin rigidification and dimerization. *Nature.* 380:360-364.
20. Tamura K, Shan WS, Hendrickson WA, et al. (1998). Structure-function analysis of cell adhesion by neural (N-) cadherin. *Neuron.* 20:1153-1163.
21. Ozawa M, Engel J, and Kemler R. (1990). Single amino acid substitutions in one Ca2+ binding site of uvomorulin abolish the adhesive function. *Cell.* 63:1033-1038.
22. Kemler R and Ozawa M. (1989). Uvomorulin-catenin complex: cytoplasmic anchorage of a calcium dependent cell adhesion molecule. *Bioessays.* 11:88-91.
23. Pokutta S. (1994). Conformational changes of the recombinant extracellular domain of E-cadherin upon calcium-binding. *Eur J Biochem.* 223:1019-1026.
24. Nagafuchi A and Takeichi M. (1988). Cell binding function of E-cadherin is regulated by the cytoplasmic domain. *EMBO J.* 7:3679-3684.
25. Ozawa M, Ringwald M, and Kemler R. (1990). Uvomorulin-catenin complex formation is regulated by a specific domain in the cytoplasmic region of the cell adhesion molecule. *Proc Natl Acad Sci U S A.* 87:4246-4250.
26. Brieher WM, Yap AS, and Gumbiner BM. (1996). Lateral dimerization is required for the homophilic binding activity of C-cadherin. *J Cell Biol.* 135:487-496.
27. Nagafuchi A and Takeichi M. (1989). Transmembrane control of cadherin-mediated cell adhesion: a 94 kDa protein functionally associated with a specific region of the cytoplasmic domain of E-cadherin. *Cell Regul.* 1:37-44.
28. Kemler R. (1993). From cadherins to catenins: Cytoplasmic protein interactions and regulation of cell adhesion. *Trends Genet.* 9:317-321.
29. Potter E, Bergwitz C, and Brabant G. (1999). The cadherin-catenin system: implications for growth and differentiation of endocrine tissues. *Endocr Rev.* 20:207-239.
30. Knudsen K, Soler A, Johnson K, and Wheelock M. (1995). Interaction of alpha-actinin with the cadherin/catenin cell-cell adhesion complex via alpha-catenin. *J Cell Biol.* 130:67-77.
31. Balsamo J, Leung T, Ernst H, *et al.* (1996). Regulated binding of a PTP1B-like phosphatase to N-cadherin: control of cadherin mediated adhesion by dephos-

phorylation of beta-catenin. *J Cell Biol.* 134:801-813.
32. Balsamo J, Arregui C, Leung T, and Lilien J. (1998). The nonreceptor protein tyrosine phosphatase PTP1B binds to the cytoplasmic domain of N-cadherin and regulates the cadherin-actin linkage. *J Cell Biol.* 143:523-532.
33. Witcher LL, Collins R, Puttagunta S, *et al.* (1996). Desmosomal cadherin binding domains of plakoglobin. *J Biol Chem.* 271:10904-10909.
34. Haegel H, Larue L, Ohsugi M, *et al.* (1995). Lack of beta-catenin affects mouse development at gastrulation. *Development.* 121:3529-3537.
35. Downing JR and Reynolds AB. (1991). PDGF, CSF-1, and EGF induce tyrosine phosphorylation of p120, app60 src transformation associated substrate. *Oncogene.* 6:607-613.
36. Daniel JM and Reynolds AB. (1995). The tyrosine kinase substrate p120cas binds directly to E-cadherin but not to the adenomatous polyposis coli protein or alpha-catenin. *Mol Cell Biol.* 15:4819-4824.
37. Shibamoto S, Hayakawa M, Takeuchi K, *et al.* (1995). Association of p120cas, a tyrosine kinase substrate, with E-cadherin/catenin complexes. *J Cell Biol.* 128:949-957.
38. Yap AS, Niessen CM, and Gumbiner BM. (1998). The juxtamembrane region of the cadherin cytoplasmic tail supports lateral clustering, adhesive strengthening, and interaction with p120ctn. *J Cell Biol.* 141:779-789.
39. Papkoff J. (1997). Regulation of complexed and free catenin pools by distinct mechanisms. Differential effects of Wnt-1 and v-Src. *J Biol Chem.* 272:4536-4543.
40. Yap AS, Brieher WM, Pruschy M, and Gumbiner BM. (1997). Lateral clustering of the adhesive ectodomain: A fundamental determinant of cadherin function. *Curr Biol.* 7:308-315.
41. Tomschy A, Fauser C, Landwehr R, and Engel J. (1996). Homophilic adhesion of E-cadherin occurs by a co-operative two-step interaction of N-terminal domains. *EMBO J.* 15:3507-3514.
42. Kinch MS, Petch L, Zhong C, and Burridge K. (1997). E-cadherin engagement stimulates tyrosine phosphorylation. *Cell Adhes Commun.* 4:425-437.
43. Braga VM, Machesky LM, Hall A, and Hotchin NA. (1997). The small GTPases Rho and Rac are required for the establishment of cadherin dependent cell-cell contacts. *J Cell Biol.* 137:1421-1431.
44. Levenberg S, Katz BZ, Yamada K, and Geiger B. (1998). Long-range and selective autoregulation of cell-cell or cell-matrix adhesions by cadherin or integrin ligands. *J Cell Sci.* 111:347-357.
45. Cadigan KM and Nusse R. (1997). Wnt signaling: A common theme in animal development. *Genes Dev.* 11:3286-3305.
46. Dale TC. (1998). Signal transduction by the Wnt family of ligands. *Biochem J.* 329:209-223.
47. Papkoff J, Rubinfeld B, Schryver B, and Polakis P. (1996). Wnt-1 regulates free pools of catenins and stabilizes APC-catenin complexes. *Mol Cell Biol.* 16:2128-2134.
48. Behrens J, Von Kries JP, Kuhl M, *et al.* (1996). Functional interaction of beta-catenin with the transcription factor LEF-1. *Nature.* 382:638-642.
49. Molenaar M, VandeWetering M, Oosterwegel M, *et al.* (1996). XTcf-3 transcription factor mediates beta-catenin-induced axis formation in Xenopus embryos. *Cell.* 86:391-399.
50. Aberle H, Bauer A, Stappert J, *et al.* (1997). Beta-catenin is a target for the ubiquitin-proteasome pathway. *EMBO J.* 16:3797-3804.
51. Korinek V, Barker N, Morin PJ, *et al.* (1997). Constitutive transcriptional activation by a beta-catenin-Tcf complex in APCC-/- colon carcinoma. *Science.* 275:1784-1787.
52. Morin PJ, Sparks AB, Korinek V, *et al.* (1997). Activation of beta-catenin-Tcf signalling in colon cancer by mutations in beta-catenin or APC. *Science.* 275:1787-1790.
53. Rubinfeld B, Robbins P, El-Gamil M, *et al.* (1997). Stabilization of beta-catenin by genetic defects in melanoma cell lines. *Science.* 275:1790-1792.
54. Melkonyan HS, Chang WC, Shapiro JP, *et al.* (1997). SARPs: A family of secreted apoptosis-related proteins. *Proc Natl Acad Sci USA.* 94:13636-13641.
55. Van der Heyden MA, Rook MB, Hermans MM, *et al.* (1998). Identification of connexin43 as a functional target for Wnt signaling. *J Cell Sci.* 111:1741-1749.
56. Brannon M and Kimelman D. (1996). Activation of siamois by the Wnt pathway. *Dev Biol.* 180:344-347.
57. He TC, Sparks AB, Rago C, *et al.* (1998). Identification of c-MYC as a target of the APC pathway. *Science.* 281:1509-1512.
58. Novak A, Hsu SC, Leung-Hagesteijn C, *et al.* (1998). Cell adhesion and the integrin-linked kinase regulate the LEF-1 and beta-catenin signaling pathways. *Proc Natl Acad Sci USA.* 95:4374-4379.
59. George-Weinstein M, Gerhart J, Blitz J. (1997). N-cadherin promotes the commitment and differentiation of skeletal muscle precursor. *Dev Biol.* 185:14-24.
60. Linask KK, Knudsen KA, and Gui YH. (1997). N-cadherin-catenin interaction: Necessary component of cardiac cell compartmentalization during early vertebrate heart development. *Dev Biol.* 185:148-164.
61. Nakagawa S and Takeichi M. (1998). Neural crest emigration from the neural tube depends on regulated cadherin expression. *Development.* 125:2963-2971.
62. Islam S, Carey TE, Wolf GT, *et al.* (1996). Expression of N-cadherin by human squamous carcinoma cells induces a scattered fibroblastic phenotype with disrupted cell-cell adhesion. *J Cell Biol.* 135:1643-1654.
63. Moll R, Mitze M, Frixen UH, and Birchmeier W. (1993). Differential loss of E-cadherin expression in infiltration ductal and lobular breast carcinomas. *Am J Pathol.* 143:1731-1742.
64. Berx G, Cleton-Jansen AM, Nollet F, *et al.* (1995). E-cadherin is a tumor/invasion suppressor gene mutated in human lobular breast cancers. *EMBO J.* 14:6107-6115.
65. De Leeuw WJ, Berx G, Vos CB, *et al.* (1997). Simultaneous loss of E-cadherin and catenins in invasive lobular breast cancer and lobular carcinoma in situ. *J Pathol.* 183:404-411.
66. Schipper JH, Frixen UH, Behrens J, *et al.* (1991). E-cadherin expression in squamous cell carcinomas of head and neck: inverse correlation with tumor dedifferentiation and lymph node metastasis. *Cancer Res.* 51:6328-6337.
67. Schipper JH, Unger A, and Jahnke K. (1994). E-cadherin as a functional marker of the differentiation and invasiveness of squamous cell carcinoma of the head and neck. *Clin Otolaryngol.* 19:381-384.
68. Gabbert HE, Mueller W, Schneiders A, *et al.* (1996). Prognostic value of E-cadherin expression in 413 gastric carcinomas. *Int J Cancer.* 69:184-189.
69. Brabant G, Hong-Vu C, Cetin Y, *et al.* (1993). E-cadherin: A differentiation marker in thyroid malignancies. *Cancer Res.* 53:4987-4993.
70. Scheumann GF, Hoang-Vu C, Cetin Y, *et al.* (1995). Clinical significance of E-cadherin as a prognostic marker in thyroid carcinomas. *J Clin Endocrinol Metab.* 80:2168-2172.
71. Otto T, Rembrink K, Meyer-Schwickerath M, and Rubben H. (1993). E-cadherin: a marker for differentiation and invasiveness in prostatic carcinoma. *Urol Res.* 21:359-362.
72. Guilford P, Hopkins J, Harraway J, *et al.* (1998). E-cadherin germline mutations in familial gastric cancer. *Nature.* 392:402-405.
73. Navarro P, Lozano E, and Cano A. (1993). Expression of E- or P-cadherin is not sufficient to modify the morphology and the tumorigenic behaviour of murine spindle carcinoma cells. Possible involvement of Plakoglobin. *J Cell Sci.* 105:923-934.
74. Kantak SS and Kramer RH. (1998). E-cadherin regulates anchorage-independent growth and survival in oral squamous cell carcinoma cells. *J Biol Chem.* 273 :16953-16961.
75. Day ML, Zhao X, Vallorosi CJ, *et al.* (1999). E-cadherin mediates aggregation-dependent survival of prostate and mammary epithelial cells through the retinoblastoma cell cycle control pathway. *J Biol Chem.* 274:9656-9664.
76. Pece S, Chiariello M, Murga C, and Gutkind JS. (1999). Activation of the Protein Kinase Akt/PKB by the formation of E-cadherin-mediated cell-cell junctions. *J Biol Chem.* 274:19347-19351.
77. Makrigiannakis A, Coukos G, Christofidou-Solomidou M, *et al.* (1999). N-cadherin-mediated human granulosa cell adhesion prevents apoptosis: a role in follicular atresia and luteolysis? *Am J Pathol.* 154:1391-406.
78. Peluso J and Pappalardo A. (1994). Progesterone and cell-cell adhesion interact to regulate rat granulosa cell apoptosis. *Biochem Cell Biol.* 72:547-551.
79. Peluso J, Pappalardo A, and Trolice M. (1996). N-cadherin-mediated cell contact inhibits granulosa cell apoptosis in a progesterone independent manner. *Endocrinology.* 137:1196-1203.
80. Peluso JJ. (1997). Putative mechanism through which N-cadherin-mediated cell contact maintains calcium homeostasis and thereby prevents ovarian cells from undergoing apoptosis. *Biochem Pharmacol.* 54:847-853.
81. Munro SB, Duclos AJ, Jackson AR, *et al.* (1996). Characterization of cadherins expressed by murine thymocytes. *Cell Immunol.* 169:309-312.
82. Muller KM, Luedecker CJ, Udey MC, and Farr AG. (1997). Involvement of E-cadherin in thymus organogenesis and thymocyte maturation. *Immunity.* 6:257-264.
83. Lee MG, Tang A, Sharrow SO, and Udey MC. (1994). Murine epidermal T cells (DETC) express the homophilic adhesion molecule E-cadherin. *Epith Cell Biol.* 3:149-155.
84. Wayner EA, Hoffstrom B, and Pittlekow M. (1994). T lymphocyte adhesion to keratinocytes: cooperative role for the integrin receptor alpha3beta1 and E-cadherin. *J Invest Dermatol.* 102:524.
85. Cepek K, Shaw S, Parker C, *et al.* (1994). Adhesion between epithelial cells and T lymphocytes mediated by E-cadherin and the alpha E Beta 7 integrin. *Nature.* 372:190-193.
86. Karecla PI, Bowden SI, Green SJ, and Kilshaw PJ. (1995). Recognition of E-cadherin on epithelial cells by the mucosal T cell integrin alpha M290 beta 7 (alpha E beta 7). *Eur J Immunol.* 25:852-856.
87. Karecla PI, Green SJ, Bowden SJ, (1996). Identification of a binding site for integrin alphaEbeta7 in the N-terminal domain of E-cadherin. *J Biol Chem.* 271:30909-30915.
88. Trollmo C, Nilsson IM, Sollerman C, and Tarkowski A. (1996). Expression of the mucosal lymphocyte integrin alpha E beta 7 and its ligand E-cadherin in the synovium of patients with rheumatoid arthritis. *Scand J Immunol.* 44:293-298.
89. Jakob T and Udey MC. (1998). Regulation of E-cadherin mediated adhesion in Langerhans cell-like dendritic cells by inflammatory mediators that mobilize Langerhans cells in vivo. *J Immunol.* 160:4067-4073.
90. Kripke ML, Dunn CG, Jeevan A, *et al.* (1990). Evidence that cutaneous antigen-presenting cells migrate to regional lymph nodes during contact sensitization. *J Immunol.* 145:2833-2836.
91. Jakob T, Saitoh A, and Udey MC. (1997). E-cadherin-mediated adhesion involving Langerhans cell-like dendritic cells expanded from murine fetal skin. *J Immunol.* 159:2693-2701.
92. Armeanu S, Buhring HJ, Reuss-Borst M, *et al.* (1995). E-cadherin is functionally involved in the maturation of the erythroid lineage. *J Cell Biol.* 131:243-249.
93. Cepek KL, Rimm DL, and Brenner MB. (1996). Expression of a candidate cadherin in T lymphocytes. *Proc Natl Acad Sci USA.* 93 :6567-6571.
94. Tsutsui J, Moriyama M, Arima N, *et al.* (1996). Expression of cadherin-catenin complexes in human leukemia cell lines. *J Biochem.* 120:1034-1039.
95. Kawamura-Kodama K, Tsutsui J, Suzuki ST, *et al.* (1999). N-cadherin expressed on malignant T cell lymphoma cells is functional, and promotes heterotypic adhesion between the lymphoma cells and mesenchymal cells expressing N-cadherin. *J Invest Dermatol.* 112:62-66.
96. Monier-Gavelle F and Duband JL. (1997). Cross talk between adhesion molecules: control of N-cadherin activity by intracellular signals elicited by beta1 and beta3 integrins in migrating neural crest cells. *J Cell Biol.* 137:1663-1681.

In the Literature

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This section of News and Views will present updates of recent advances in the medical and scientific literature.

Oocytes Matured *in vitro* May Improve Current Infertility Therapy

The polycystic ovarian syndrome (PCOS) is an incompletely understood disorder characterized by infertility due to anovulation, hyperandrogenism, and ovaries containing multiple immature cystic follicles. Conventional treatment for infertility due to PCOS has involved ovulation induction using agents such as clomiphene and gonadotropins. However, infertility due to PCOS is often refractory to these drugs. When a response is achieved, patients are at risk of developing ovarian hyperstimulation syndrome, which may result in ascites, oliguria, electrolyte disturbances, and thromboembolism. Chiang and colleagues at the Royal Victoria Hospital in Montreal have reported that modification of the technique of *in vitro* fertilization (IVF) with intracytoplasmic sperm injection (ICSI) can improve success rates in women with PCOS. The modification consists of inducing maturation of the oocyte *in vitro* prior to fertilization. The 20 women in their study were treated for 10 days with progesterone to produce a withdrawal bleed, followed 10-14 days later by a dose of human chorionic gonadotropin (hCG) to induce ovulation. After another 36h, eggs were harvested by aspiration from the surfaces of their ovaries. The oocytes were then allowed to mature *in vitro* in a medium enriched with gonadotropins and the patient's own serum. The investigators found that 84% of 249 oocytes (retrieved from the 20 women in a total of 25 treatments of IVF with ICSI) matured successfully *in vitro*. The pregnancy rate was 40% (10 pregnancies in 25 treatments). Moreover, three women whose infertility had previously been unsuccessfully treated with conventional IVF became pregnant using this new method. This evidence indicates that a better infertility treatment may soon be widely available to women with PCOS, in whom conventional infertility therapies are often not successful.

(Chiang R-C, Gülekli B, Buckett WM, and Tan S-L. NEJM. (1999). 341: 1624-1626)

Mice Genetically Protected Against Oxidative Damage Live Longer

It has often been suspected that aging and senescence may in part result from the cumulative cellular effects of oxidative stress. In the mid-1990s, it was discovered that nematode worms, yeast, and fruit flies protected from oxidative stress by robust cellular antioxidant mechanisms have longer life spans. Now it has been shown, by Migliaccio and coworkers, that a specific mutation in mice produces a longer lifespan, also by conferring resistance to oxidative damage. This mutation is found in the gene encoding $p66^{shc}$, an adaptor protein that transduces signals from activated tyrosine kinase receptors to the nucleus. The researchers exposed mouse embryo fibroblasts (MEFs) to two forms of oxidative stress, namely ultraviolet (UV) light and hydrogen peroxide. They found that $p66^{shc}$ is serine phosphorylated in MEFs in response to these oxidative stressors. They then compared wild type MEFs with MEFs in which one or both copies of the $p66^{shc}$ gene were knocked out. Wild type MEFs underwent massive apoptosis in response to UV and peroxide. However, lower rates of apoptosis were seen among MEFs with one copy of $p66^{shc}$ knocked out, and even lower rates were seen among MEFs with both copies knocked out. Interestingly, the capacity to proliferate was retained in the surviving knockout MEFs. In an attempt to clarify the role of $p66^{shc}$ in the apoptotic response to oxida-

tive stress, the researchers investigated the interaction of the protein with p53 and p21. These proteins are known to be involved in cell cycle arrest and apoptosis in response to many insults, including oxidative damage. Further, it is known that the upregulation of p21 that occurs following exposure to peroxide or UV results from p53-dependent and –independent pathways. In this study, the researchers found that p53 was upregulated to a comparable degree in both wild type and $p66^{shc}$ knockout MEFs in response to oxidative stress. However, in $p66^{shc}$ knockout MEFs, the p21 response was partially attenuated when compared with the p21 response in wild type MEFs exposed to the same degree and type of oxidative stress. This finding suggests that the p53-independent pathway of p21 activation is disrupted by the loss of $p66^{shc}$. Further investigation revealed that knockout of p21 alone did not affect the response of the MEFs to oxidative stress, suggesting that the protective effects of $p66^{shc}$ knockout could not solely be attributed to disruption of p21 activation. As predicted by previous studies, knockout of p53 produced MEFs that were resistant to apoptosis. Taken together, these findings led the researchers to speculate that oxidative stress can activate one of two pathways: one in which p53 stimulates apoptosis and another in which p21 protects from apoptosis, through p53-dependent and –independent activation. Finally, the investigators treated wild type mice and mice with both copies of $p66^{shc}$ knocked out with paraquat, a drug that generates intracellular superoxide anions. While 5 of 5 wild type mice died in 48 hours, only 2 of 5 knockout mice died in the same period, and one survived for several weeks. Cumulative statistical analysis showed that this difference translated into a 40% increase in lifespan in the knockout mice. These findings have at least two important implications. First, they extend the findings of previous studies which implicated a role for oxidative damage in the aging of mammals. Second, they appear to contradict the traditional evolutionary dogma that aging is a post-reproductive process: genes acting before a reproductive age to confer a shortened lifespan ($p66^{shc}$ acts both before and after reproduction) should be under great selective pressure to be eliminated from the population.

(Migliaccio E, Giorgio M, Mele S, et al. Nature. (1999). 402: 309-313)

NSAIDs Inhibit Angiogenesis *in vitro*

Angiogenesis (the formation of new blood vessels from existing ones) is a fundamental process that plays a key role in wound healing. There is also mounting evidence that it is critical in the development of cancer, by providing growing primary tumours and metastases with a source of oxygen and nutrition. Non-steroidal anti-inflammatory drugs (NSAIDs) such as indomethacin are known to be chemopreventative against colon cancer for unknown reasons. Jones and colleagues hypothesized that this effect may result from NSAID-mediated inhibition of angiogenesis. They studied the ability of NSAIDs to inhibit angiogenesis *in vitro* using rat and human endothelial cells. Both vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) stimulate angiogenesis in these cells. This effect was blocked by the addition of indomethacin, a "traditional NSAID" that inhibits both COX-1 and COX-2 isoforms of cyclooxygenase. It was also abolished by NS-398, a new COX-2-selective NSAID. It is known from previous work that the mitogen-activated protein kinase (MAP kinase) ERK2 must undergo nuclear translocation in endothelial cells for angiogenesis to occur. Both indomethacin and NS-398 inhibited the kinase activity of ERK2 (*in vitro* in a cell-free preparation); similarly, both drugs inhibited the nuclear translocation of ERK2 (as detected by immunofluorescence microscopy) in endothelial cells exposed to these drugs. Since many of the effects of NSAIDs are attributable to COX inhibition, the researchers added prostaglandin E_2 (PGE_2) and prostacyclin (PGI_2) to endothelial cell cultures. These compounds partially reversed the inhibition of angiogenesis induced by NS-398 but, intriguingly, not by indomethacin. Taken together, these findings indicate that endothelial cell prostaglandins are important for angiogenesis, but that prostaglandin-independent angiogenesis can occur and is also inhibited by non-selective NSAIDs via a pathway not involving COX-1 or COX-2. This study has at least two important ramifications. First, COX-2-selective inhibitors, which are touted as less likely to produce gastric and duodenal ulcers, may in fact inhibit the angiogenesis involved in ulcer healing. Second, the chemoprotective effect of NSAIDs against colon cancer may now, at least in part, be explained. NSAIDs may find use in the future in the prevention and/or treatment of other cancers.

(Jones MK, Wang H, Peskar BM, et al. Nature Med. (1999). 5: 1418-1423)

Importance of C-reactive Protein and Complement in Acute Myocardial Infarction

It is known that both complement components and C-reactive protein (CRP), an acute phase protein, are deposited in infarcted myocardial tissue, from both clinical and laboratory studies. Serum CRP peaks rapidly in acute illnesses associated with tissue damage and inflammation, including acute myocardial infarction (AMI). It has been shown that the peak serum CRP concentration following AMI correlates with patient outcome, with higher CRP concentrations conferring a poor prognosis. Furthermore, human CRP, but not rat CRP, is a potent activator of the classical complement pathway, a cascade of proteolytic reactions that culminates in cell membrane damage and inflammatory cell recruitment. Consequently, Griselli and co-workers hypothesized that CRP-mediated activation of the classical complement pathway may underlie a portion of the myocardial damage resulting from AMI. Experimental AMI was induced in Wistar rats by ligation of the left anterior descending (LAD)

artery. Infarctions were confirmed electrocardiographically. In the five days following the infarction, the rats were injected repeatedly with either human CRP, cobra venom factor (a protein that depletes serum complement), both, or the buffer solution. After this period, infarct sizes were measured by sectioning the myocardial tissue and treating it with nitroblue tetrazolium (NBT), which stains only viable tissue blue. Rats injected with human CRP were less well and had reproducibly larger (by 40%) infarcts than rats injected with buffer solution. In contrast, rats injected with cobra venom factor up to 24 hours prior to coronary artery ligation had infarcts that were 60% smaller than rats injected with buffer solution. Addition of human CRP to the latter experiment did not abrogate the reduction in infarct size; this indicates that the damaging effect of human CRP is dependent on the presence of complement in this model. A further experiment was conducted in which human serum amyloid protein (SAP), an acute phase protein very similar in structure to human CRP, was injected. This did not have any of the adverse effects associated with the injection of human CRP, indicating that these effects were specific to human CRP. Most interestingly, from a clinical perspective, was the finding that the addition of cobra venom factor as much as two hours after LAD ligation reduced infarct size by almost 50%. On histologic analysis, the researchers found that human CRP, rat CRP, and complement were deposited in the infarcted myocardium, and that complement components were only present if human CRP was also present. Together, these findings suggest that complement and CRP play an important role in the development of myocardial damage following AMI, and that it is possible to interfere with this process by depleting serum complement even after the onset of ischemia. Hence, they point toward a possible future therapeutic intervention for AMI.

(Griselli M, Herbert J, Hutchinson WL, et al. J Exp Med. (1999). 190: 1733-1739)

The DNA Sequence of Human Chromosome 22: The First Sequencing Landmark of the Human Genome Project

The human genome is neatly packaged into 23 pairs of chromosomes, with 22 pairs of autosomes and 1 pair of sex chromosomes. Chromosome 22 is one of the smallest human autosomes and it is comprised of 1.6 – 1.8% of the genomic DNA. It is one of the five acrocentric chromosomes. The short arm of chromosome 22 consists of the tandemly repeated ribosomal RNA genes as well as other tandem repeat arrays; however, there is no evidence of any protein encoding genes in that region. In contrast, its long arm is rich in genes compared with other chromosomes. To date, there are thought to be over twenty human disorders associated with changes to genes on this chromosome. Gene dosage alteration of chromosome 22 has been implicated in a number of human diseases, including cat eye syndrome, velocardiofacial/DiGeorge syndrome, schizophrenia, and spinocerebellar ataxia 10. The sequence that was reported in a recent issue of *Nature* consists of 33.4 million bases containing at least 545 genes. However, the sequences of eleven small gaps were unable to be determined with existing cloning techniques. Nevertheless, this effort generated the largest contiguous segment of DNA sequence known to date and it represents the first sequencing landmark of the human genome project. In practical terms, this DNA sequence will provide a framework within which we will be able to map differences between individuals that make us unique, as well as changes that represent disease states. The next challenge following the completion of the human genome project (projected in the year 2002) is to translate this information into tangible applications.

(Dunham I, Shimizu N, Roe BA, Chissoe S, et al. Nature. (1999). 402: 489-495)

The Identification of a Promising Antibiotic Candidate

The increasing resistance of pathogenic microbes to antibiotics raises the possibility of an alarming scenario in which doctors are powerless to treat many bacterial infections. Even vancomycin, a longtime antibiotic of last resort, seems to be losing its effect: vancomycin resistance has emerged in enterococci. Researchers have discovered a promising replacement antibiotic that has been used as a food preservative for over fifty years. The compound, nisin, is a peptide of the lantibiotic family (lanthionine-containing antibiotics) and it is produced by certain strains of *Lactococcus lactis*, the bacteria that can turn milk sour. Nisin is known to be non-toxic to humans yet it possesses high bactericidal activity. Its mechanism of action was thought to be permeabilization of the bacterial plasma membrane through the formation of pores. In a recent issue of *Science*, a Dutch-German team of scientists demonstrated that nisin binds the membrane-anchored cell wall precursor Lipid II, the same target as vancomycin. First, the researchers found that nisin resembles magainin, a peptide antibiotic derived from frogs, in that it kills *Micrococcus flavus* bacteria by forming pores in the cell membrane. Secondly, further experiments showed that vancomycin inhibited nisin's membrane leakage activity against intact bacterial cells but it had no effect on magainin. These results suggested that vancomycin and nisin are competing for the same target, namely Lipid II. In a series of tested systems, the interaction between nisin and Lipid II was demonstrated to be specific; however the precise mechanism of pore formation through Lipid II remains to be elucidated. The low effective dose of nisin makes it desirable compared to other known peptide antibiotics. In addition, no nisin-resistant bacterium has been identified to date. This discovery holds a promise that nisin may one day replace vancomycin as a broad-range antibiotic.

(Breukink E, Wiedemann I, van Kraaij C, et al. Science. (1999). 286: 2361-2364)

Primate Cloning by Embryo Splitting

Animal cloning was merely a concept in science fiction until the birth of the sheep "Dolly" in 1997. This remarkable achievement was followed by the successful cloning of cattle, mice, and goats. Cloning by nuclear transfer using blastomere nuclei in macaques has also been described; however, the nuclear transfer technique results in genetic chimeras with mitochondrial heterogeneity. In a recent issue of *Science*, Chan and colleagues reported the birth of the first non-human primate clone produced by embryo splitting. One hundred and seven rhesus embryos were split to create 368 multiples. Specifically, an eight-cell embryo was split to produce a set of identical quadruplet embryos each consisting of two blastomeres. A pair of the quadruplet embryos was then transferred into two fertile surrogates; both became pregnant. One gestated a pregnancy with a placental sac devoid of fetal tissue while the other pregnancy was uneventful and culminated in the birth of Tetra, the first rhesus monkey cloned by embryo splitting, at 157 days. Microsatellite-based polymerase chain reaction demonstrated that the "blighted" pregnancy and Tetra were genetically identical. A total of thirteen embryo transfers were performed, which resulted in four pregnancies (31% success rate), 1 fetal sac, and one live birth (8%). In contrast, in vitro fertilization controls produced eight pregnancies (53%), 10 fetal sacs, and 6 live births (40%). Apoptosis was found to be higher in split embryos (especially in the inner cell mass) than in controls, likely contributing to the higher miscarriage rate. Quadruplets appear to be the upper viability limit for offspring survival. Furthermore, larger sets of identical embryos showed decreased developmental potential. Cloning by embryo splitting produces genetically identical offspring, which are valuable tools in the study of disease and innovative therapies.

(Chan AWS, Dominko T, Luetjens CM, et al. Science. (2000). 287: 317-319)

Correlation Between the Risk of Spontaneous Abortion and Caffeine Consumption

The consumption of caffeine during pregnancy and its possible relationship with spontaneous abortion is a controversial health issue. Some studies have indicated that moderate to heavy caffeine intake is associated with a risk of fetal loss while others have found no evidence of increased risk. Previous studies used questionnaires to ascertain caffeine consumption, which may not be an accurate assessment. In a nested-case control study, Klebanoff and colleagues used a biological marker, serum paraxanthine (the primary caffeine metabolite) to measure the amount of caffeine present in the body. The serum paraxanthine levels of 591 women who had spontaneous abortions at less than 140 days gestation and 2558 matched women from the same clinic who gave birth to live infants at 28 weeks gestation or later, were measured and compared. Results demonstrated that the mean concentration of serum paraxanthine was significantly higher in the women who had spontaneous abortions than that in the controls (752 vs. 583 ng/mL, $p<0.001$). However, the risk of spontaneous abortion is not increased until extremely high serum paraxanthine levels (1845 ng/mL) are reached. Since there is no precise way to equate serum paraxanthine level with the amount of caffeine consumed, it is not yet possible to determine how much caffeine is safe during pregnancy. A previous study by the same authors found that the highest caffeine intake was 1530 mg (approximately 15 cups of coffee) and the highest measured serum paraxanthine concentration was found to be 1165 ng/ml (substantially lower than the 1845 ng/ml value in this study). These high levels of caffeine intake may be reflective of the lifestyle in the 1960s (when the samples were obtained), and the consumption of such high levels of caffeine is probably not a common practice today. In summary, the results of this study suggest that the risk of spontaneous abortion is associated with extremely high caffeine consumption and that moderate consumption is unlikely to constitute a significant risk.

(Klebanoff MA, Levine RJ, DerSimonian R, et al. NEJM. (1999). 341: 1639-1644)

The Hope Trial: Effects of an ACE Inhibitor on Death from Cardiovascular Causes, Myocardial Infarction, and Stroke in High Risk Patients

(reviewed by Marshall Hay, B.Sc. 0T1)

Recently, New England Journal of Medicine's web site (www.nejm.org) published a paper studying the effects of ACE inhibitors in high-risk patients. The online publication preceded its journal appearance (expected to appear January 20, 2000) because of the potential therapeutic implications. As described elsewhere, the Heart Outcomes Prevention Evaluation (HOPE) Study Investigators examined 9297 high risk patients (55 years of age or older) who had vascular disease or diabetes plus at least one other cardiovascular risk factor (hypertension, elevated total cholesterol levels, low HDL cholesterol levels, smoking, or microalbuminuria) who were not known to have a low ejection fraction or heart failure. Subjects were randomly assigned to receive ramipril (100 mg po OD) or placebo for a mean of five years. Results demonstrated an overall reduction of 22 percent in the primary outcome of myocardial infarction, stroke, or death from cardiovascular causes. Additionally, those receiving ramipril had higher rates of coronary revascularization, lower rates of cardiac arrest and heart failure, and lower rates of complications related to diabetes and of diabetes itself. These results may significantly broaden the spectrum of patients who are likely to benefit from ACE inhibitors.

(The HOPE Study Investigators. NEJM. (2000). 342: 145-153)

In the Media

Edward C W. Leung, B.Sc. (0T2)

Drug Firm Threatens to Prosecute MD Over Unfavorable Guidelines

Dr. Anna Holbrook, at the Centre for the Evaluation of Medieines at St. Joseph's Hospital in Hamilton, was asked by the Ontario Ministry of Health to chair a panel of experts to formulate guidelines on the treatment of heartburn, ulcers and related eonditions. When the panel eoneluded in the guidelines that Losec was very similar to two other uleer drugs in the same elass, and that these drugs could be used interehangeably, AstraZeneca PLC, the manufaeturer of Losec, objeeted. On Feb. 26, 1998, Dr. Holbrook received a letter from a Toronto law firm, Smart and Biggar, representing AstraZeneea, threatening legal aetion against Dr. Holbrook if the guidelines were distributed.

The Globe and Mail, Nov 17, 1999, A1,5

Family of 10 Weeks' Pregnant Brain Dead Woman Wants to Keep Her Body Alive for Fetus

Twenty-five year-old Sophia Park was admitted to Toronto Western Hospital on November 17, 1999 with tubereulous meningitis. She was misdiagnosed multiple times sinee September when she first presented with symptoms of tubereulosis. After unsueeessful treatment at the Western, she was declared brain dead on November 27, 1999. Ms. Park's family wanted to keep her body alive for 20 weeks until the 10-week-old fetus she was earrying could be delivered.

According to the *National Post*, family members elaimed that doetors and nurses at Toronto Western Hospital were trying to subvert the families' wishes to maintain life support to save the fetus. To provide "hope for the family," the *National Post* ran a separate artiele deseribing a British woman in a meningitis-related eoma giving birth to a 33-week infant in June, and an American woman giving birth to a healthy baby boy while in a six-month-long "brain death" coma.

The Globe and Mail foeused its discussion on the viability of the fetus and the limited resourees available in a hospital setting. In contrast, the *Toronto Star* presented selected statements from different interviewees: "Doetors have no obligation to treat a dead person," and "This is a fetus. It's not at a stage where it ean exist on its own. It takes away the total eontrol of the woman. If we go down this road, there's no telling what will be next."

Unfortunately, the ethieal debate was curtailed when an ultrasound performed on December 3, 1999 showed that the fetus Sophia Park was earrying had died.

The Globe and Mail, Dec 3, 1999, A18
The Toronto Sun, Dec 3, 1999, 5; Dec 4, 1999, 7
The Toronto Star, Dec 2, 1999, A1,26; Dec 4, 1999, A16
The National Post, Dec 2, 1999, A1,9; Dec 3, 1999, A12

Emergency Room Crisis Across the Country

At one point on Deeember 6, 1999, 23 out of 25 hospital emergeney rooms in the Toronto area were on restrieted aeeess, 9 were on redirect and 14 were on erit-

ical-care bypass. Only Oshawa General and the Hospital for Sick Children remained unaffected. Once, when one hospital removed its redirect order, 11 ambulances arrived within 20 minutes. *The Globe and Mail* described the ambulance attendants as "vultures circling, waiting for someone to die" to gain access to a free bed in the ER.

The *Toronto Sun* and the *Globe and Mail* agreed that the problem is due to the closure of almost 11,000 hospital beds, which began a decade ago in anticipation of increased home-care nurses and new construction of long-term-care and rehabilitation facilities. Ontario Health Minister Elizabeth Witmer claimed that several projects to build facilities with long-term-care beds have been held up by municipal approvals and construction delays.

The emergency rooms in the Toronto area continued to be swamped from January 1 to January 3, 2000; however, more people were using after-hours clinics to alleviate the load in hospital emergency rooms. The ER crisis was affecting hospitals in cities all across the country, including Vancouver, Montreal, and Winnipeg. Calgary, however, did not experience this problem. *The Globe and Mail* suggested that the flu prevention program begun 2 years ago in Calgary's nursing homes prevented flu outbreaks and kept nursing homes open, thereby freeing up hospital beds.

The *Toronto Star* published a separate article arguing that the reduced number of house calls made by physicians in the past few years contributed partly to the ER crisis. Ontario doctors are paid at a reduced rate for house calls if the total number of house calls exceed 20% of a doctor's monthly number of patients. According to one physician, Dr. Alan Fegelman, he would lose $1,200 by making an additional house call because of the current fee schedule.

The Globe and Mail also pointed out that the closing of doctors' and specialists' offices during the holiday season, and the increased number of patients with the flu this past season aggravated the ER situation. The *National Post* stated that the Quebec government's policy of placing quotas on the number of prospective doctors and nurses accepted into universities also contributed to the manpower shortage experienced in the recent ER crisis in Montreal.

In response to the ER crisis, the Ontario government has announced a $23-million 10-point action plan. Four regional coordinators will direct ambulances to open hospitals in the Toronto area. At least one hospital in each region will be available to ambulance patients. Up to 197 flex beds will be provided to take hospital patient overflow. The Ontario government will devote $6.1 million to care for more patients in interim long-term-care beds. Construction of long-term-care facilities will be fast-tracked. Another $730,000 will be devoted to free flu shots for all workers in hospitals, long-term-care facilities, home-care agencies and emergency services. The government will also dedicate $3 million to hire specially trained ambulance staff to move critical-care patients between facilities.

The Globe and Mail, Dec 15, 1999, A6; Jan 5, 2000, A1,2,3.
The National Post, Jan 04, 2000, A18; Jan 10, 2000, A6.
The Toronto Sun, Dec 7, 1999, 7; Dec 21, 1999, 3; Jan 5, 2000, 7; Jan 6, 2000, 2; Jan 9, 2000, 41.
The Toronto Star, Dec 14, 1999, A1,20; Jan 3, 2000, A1,11; Jan 4, 2000, A1,11.

Tories and OMA Begin Negotiation of New Collective Agreement

On Jan 10, 2000, representatives of the Ontario Medical Association began formal negotiations with government officials on a new collective agreement to replace the current one which expires March 31, 2000. While physicians are looking for a fee increase, the government is attempting to minimize health costs. However, the key negotiation issue is predicted to be the pace of primary-care reform.

The government wants to implement the recommendations made by the Health Services Restructuring Commission to introduce "rostering" into primary-care reform as soon as possible. "Rostering" brings groups of 6 or 8 family physicians and several nurse practitioners together with one of the doctors on call at any time to service a set roster of patients. These primary health-care group practices are known as PCGs. Physicians in PCGs will be paid by salaries instead of a fee-for-service schedule.

According to the *Toronto Star*, while rostering is intended to reduce pressure on emergency rooms, ensure continuity of care, encourage preventative medical practice, and cut costs; the idea has been met with tremendous resistance. Firstly, pilot projects involving various forms of rostering, currently underway in parts of Ontario, have not been completed. The OMA is determined not to allow further expansion of rostering until the results of the current pilot projects are available. Second, the public may not accept rostering, as it is similar to the unpopular health maintenance organizations (HMOs) in the United States.

The Globe and Mail also pointed out that once patients had

signed up with a doctor, they would not be able to see family physicians outside the PCG. The entire patient file must be transferred if patients want to change to a new doctor.

It remains to be seen whether the Tories have the political will to introduce primary-care reform, a move that was resisted by all political parties in the past few terms, and a move that could potentially trigger a physicians' strike.

The Toronto Star, Jan 8, 2000, J2.
The Globe and Mail, Dec 23, 1999, A12.

Poison Pen Letters Plague The Hospital for Sick Children

Between October 1998 and May 1999, when the conflicts between Dr. Nancy Olivieri and the Hospital for Sick Children were escalating, three colleagues and supporters of Dr. Olivieri – Drs. Peter Durie, Brenda Gallie and Helen Chan – received five poison pen letters. The recipients of these letters hired a private investigator who uncovered evidence that the anonymous writer was Dr. Gideon Koren, head of the hospital's Division of Clinical Pharmacology/Toxicology. Presented with the new evidence, the Hospital for Sick Children subsequently hired Toronto harassment lawyer Barbara Humphrey to investigate the findings. On December 20, 1999, Dr. Koren confessed to having authored the letters and was promptly suspended.

In the letters, Dr. Koren described Dr. Olivieri and her supporters as a "group of pigs" and "unethical." He also called Dr. Olivieri a "borderline genius," wondering what it would take to turn her into a "Mainstream Genius." In addition, Dr. Koren told Dr. Durie, "We all have experienced in one or another your mesanthropy [he meant misanthropy] and a British version of a foul air balloon," and that Durie was "contaminating our air and fabric." Dr. Koren also told Durie, "We are all quite eager to see you leaving."

Subsequent to his confession, Dr. Koren apologized to all four doctors involved. He also resigned from his positions as head of the hospital's Population Health-Sciences Program and Pharmacology/Toxicology Division, and as deputy director of the university's Clinical Pharmacology Program. He remains the director of a pregnancy information program, Motherisk, and has a clinical appointment at the hospital and a full-time faculty appointment at the university.

On January 4, 2000, the *Toronto Star* published new allegations against Dr. Koren, made by Dr. Olivieri's lawyer, Clayton Ruby. Ruby claimed that Dr. Koren fabricated a letter from Dr. Michael Lishner, director of the Department of Medicine at Tel Aviv University's Sapir Medical Centre. In the letter, Dr. Lishner supported the view that Dr. Olivieri failed to advise patients in a timely way that the drug, deferiprone, could cause severe side effects.

The forgery accusations were immediately dismissed when Dr. Lishner authenticated his authorship of the letter. Mr. Ruby apologized for his unfounded allegation on January 7, 2000. However, the false accusations broke Dr. Koren's silence. In an interview with the *National Post*, Dr. Koren claimed that Dr. Olivieri defamed him during their protracted, bitter scientific dispute about the merits of the drug, deferiprone. This is consistent with the findings of the 312-page report from Barbara Humphrey as commissioned by the Hospital for Sick Children. According to the *Toronto Star*, the report indicated that "Koren was upset over allegations by Olivieri and her supporters that he was trying to help the drug company Apotex Inc., get the drug licensed."

The *National Post* quoted a substantial portion of Humphrey's report in a December 27, 1999 article. The report indicated that on June 1, 1999, Drs. Olivieri and Durie removed a computer they believed Dr. Koren may have used to write the anonymous letters and took it to Dr. Durie's office. The report purportedly identified seven separate events since 1996 when Dr. Koren felt under attack. According to the article, on two separate occasions, Dr. Koren "appealed to the hospital administration for help in combating the Olivieri camp's campaign against him." The report also indicated that the recipients of the poison pen letters "had been pursuing very direct and public" challenges to his professionalism and reputation.

As of the writing of this article, the disciplinary hearing of Dr. Koren at the Hospital for Sick Children has been delayed to give Dr. Koren time to study and respond to new allegations submitted by Olivieri's lawyers.

The National Post, Dec 21, 1999, A1,2; Dec 22, 1999, A3; Dec 23, 1999, A7; Dec 27, 1999, A1,8; Dec 30, 1999, A4; Jan 07, 2000, A1,4.
The Toronto Sun, Dec 22, 1999, 5; Dec 23, 1999, 10; Dec 31, 1999, 19; Jan 5, 2000, 8; Jan 8, 2000, 23.
The Toronto Star, Dec 22, 1999, A2; Dec 23, 1999, D3; Dec 24, 1999, E5; Dec 26, 1999, A42; Jan 1, 2000, D3; Jan 4, 2000, A2; Jan 5, 2000, A20; Jan 8, 2000, A20.
The Globe and Mail, Dec 21, 1999, A1,7; Dec 23, 1999, A7; Jan 5, 2000, A17.

Prolific Scientist Profiles

An Interview with Dr. Tak Wah Mak

Susan Quesnel, M.Sc. (0T2)

Tak Wah Mak initially studied chemical engineering at the University of Wisconsin. Finding it too rigid and mechanistic, he switched to chemistry and biochemistry. He was prepared to enter medical school after graduating, in no small part because this was his mother's wish, but his plans changed after he got a taste of the world of research. Perhaps if he had not graduated in January and begun working in a cancer research lab as a technician, he never would have known how research would grow on him. Instead of going to medical school he enrolled as a graduate student.

Dr. Mak received his Ph.D. in Biochemistry from the University of Alberta in 1972. Since 1974, he has been a senior staff scientist at the Ontario Cancer Institute/Princess Margaret Hospital and has been a member of the Department of Medical Biophsyics and the Department of Immunology at the University of Toronto since 1984. Dr. Mak is well known for his part in the cloning of the T cell receptor in 1984. Using subtractive hybridization, a human mRNA was identified that was specifically expressed in T cells, and not B cells. Dr. Mak is also recognized as a leader in the development of knockout mice for the analysis of gene function. In the eyes of many, his contributions make him worthy of receiving a Nobel Prize, an event that seems highly probable. In the meantime, he has received many prestigious international honours, including the Gairdner International Award in 1989.

Dr. Mak has made significant contributions in the areas of virology, immunology, genetics, and cancer signaling. Over the years, the research pursued in his laboratory has branched out into exploring the pathogenesis of cancer. The extent of his international recognition becomes obvious as we begin the interview. He points to a newspaper on the table in his office. A subsidiary of the *Herald Tribune* in Japan had published an article about a recent finding made by his group on Hodgkin's Lymphoma. (He found out that it was picked up in the popular press only after a former student sent him the article.) His group had postulated that malignant cells secrete IL-13, which stimulates cell division in an autocrine fashion. If one were able to remove IL-13 by using an antibody, then the malignant cells would die from the deprivation of this growth factor. This approach has been demonstrated to work *in vitro*.

SQ: So when will the clinical trials begin?

TWM: Well, we're sorting out the intellectual property. Fortunately we made this finding, but unfortunately it's a very small market; large companies are not interested. There are only 10,000 new patients a year in North America. They are people of your age. But Hodgkin's has two peaks: one affects patients around 15-35, and the other affects patients over 50.

SQ: What was it particularly about the immune system that you found intriguing?

TWM: I came into the immune system through my interest in T-cell leukemia. The Ontario Cancer Institute in Toronto in the 1960s and '70s was a hotbed of individuals who were at the top of their fields. There were people like McCulloch and Till, who were Canadian heroes, interested in myeloid leukemia. There was Arthur Axelrad, who was interested in erythroid leukemia. Since I was trained with McCulloch, I decided I would study a different kind of leukemia, T cell leukemia. From that I got interested in how T cells differentiate and how T cells recognize antigens. At that time, towards the beginning of the 1980s, one of

the biggest hurdles to understanding immunology was the T cell receptor. Nobody had any idea what it was about. So we were lucky to have discovered the T cell receptor.

With the T cell receptor finally at hand, an explosion of knowledge about the immune system followed. In the next ten years, there were 15,000 papers published about the T cell receptor. New avenues for investigations were opened, which led to understanding the mechanisms by which T cells recognize antigens, but also to studying T cell selection, T cell activation, T cell down regulation, T cell anergy, and T cell death. These discoveries have permitted scientific advances in the realms of autoimmune disease, vaccination, leukemia, and many other areas. Dr. Mak hopes to achieve a better understanding of the threshold of T cell recognition of antigen and tolerance mechanisms.

TWM: In the future, we want to maneuver this very delicate balance that controls whether or not the T cell will trigger and activate in order to prevent rheumatoid arthritis, relapse of multiple sclerosis, diabetes, lupus, or whatever.

SQ: What do you think are the new frontiers for immunology research as a whole?

TWM: Immunology is a very mature field. What is intriguing is that we know that immunology affects about half of the diseases in the world, not just autoimmune diseases, but arteriosclerosis, certain cardiovascular problems, and certain kinds of cancer. So we know that it has tremendous potential. A lot of people have been scratching their heads trying to understand why 10-15% of melanoma patients at very late stages have spontaneously regressed tumours without any treatments. The regression is accompanied by inflammation at the sites of the tumour, so we know that an immune reaction is going on. And to some extent in hypernephromas, there are some patients, almost towards the end of their disease, who have tumours that suddenly disappear. Again, around the sites of the tumours, there are tremendous immune reactions going on. So we know that at least with these two diseases, in yet to be defined circumstances (molecularly), the immune system can take care of the cancer. And that is potentially so intriguing and appealing as a forefront of surgery, radiation, chemotherapy, and immunotherapy to mop up, some of the really bad ones like pancreatic or lung, or glioblastoma, but a lot of the not so bad ones, like breast cancer. Fortunately, breast cancer is rather chemo- and radiation-sensitive. But for 25-30% of patients, we cannot kill the last malignant cell. There may only be a few cells left, but even high dose chemo is still not enough. It would be nice to be able to kill the last hundred cells and perhaps we can teach our immune system to do that.

SQ: So this would be a more selective method of killing tumour cells than the other methods?

TWM: Perhaps. We have to teach our immune system to make that distinction between normal and malignant cells, which is still not trivial. And it's clear with autoimmune diseases that we need to know a lot more about what kind of threshold, why in some individuals the cells are tolerant and in others, they are not.

SQ: Over the years, your lab has branched out into exploring the pathogenesis of cancer and your group has contributed immensely to our understanding of genes that may play a role in this process, such as BRCA1 and PTEN. Although we have all of this information, we are still so far from being able to translate it to the bedside. How far do think we are from achieving this?

TWM: I think we are very close. We are still far from understanding some genes, like BRCA1, because they are probably involved in some kind of sensing of DNA damage and in the whole process of DNA repair. That's a big complicated black box that needs decades to sort out. But other genes, like PTEN, are mutated in a large number of very common cancers. This gives these genes a high level of significance. Probably all late stage glioblastomas have a mutated PTEN, as well as 30% of breast cancers, 60% of prostate cancers, 50% of endometrial cancers, and a substantial number of melanomas and thyroid cancers. Dr. Stambolic in our laboratory discovered that PTEN is involved in the PI3 kinase pathway, which is involved in many different kinds of fundamental processes, including cell division, cell survival, and angiogenesis. Uncovering pathways that directly impact the cell due to its lack of PTEN is going to lead to new targets. The pharmaceutical industry and the academic community have been concentrating on basic molecular mechanisms of cell growth and survival in the hope of uncovering targets that would be amenable to small molecules in a drug discovery. The whole idea is to try and have a rational drug design, instead of trying to kill cancer cells with the use of alkylating agents, nucleoside analogues, and DNA-binding proteins, like adriamycin, none of which are actually targeting a change that is present on a tumour cell but not on a normal cell. Therapeutic index is very important. There is not too much of a therapeutic index in a cell that has cancer versus one that doesn't if you're going to throw in just adriamycin. You want to target a particular pathway. Right now in the market, there's only been one chemotherapeutic agent that we are treating our patients with and it is used because we know the mechanism. The drug is transretinoic acid and it is used to treat patients with acute promyelocytic leukemia.

SQ: Do you think this sort of approach to drug design will be more successful than gene therapy?

TWM: I am extremely pessimistic about gene therapy for can-

cer. The delivery systems that we have are not anywhere close to making an impact. Certain types of cancer (glioblastoma, lung cancer, pancreatic cancer) are non-responsive to chemotherapeutic agents. But in cancers that do respond well, like breast cancer, we have to reduce the number of cancerous cells from 100 billion to none. Maybe radiation will take care of 6 logs, maybe chemotherapy agents will take care of another 3-4 logs, but we need to reduce the number of cancerous cells by 13 logs or so. That's the problem. If you have a breast cancer that has metastasized to the lymph nodes, that means that cancerous cells have escaped from the breast tissue and there could be anywhere from 1 million to a billion cells in body and so we must rely on chemotherapeutic agents. So I don't think that gene therapy, which will hit a percentage of the cells in the order of 50-60%, will make any impact. We basically have to get the last cell, especially in patients with end-stage disease in which the cancer cells are resistant to many different drugs and radiation. My own wife died of breast cancer. When her tumour came back the first time to the day she died, it was 7 days, with treatment. Her tumour was completely resistant to any treatment that we gave. It was like a hurricane. Nothing would stop it. The tumour probably fired all of its checkpoints. It probably had PTEN mutated and very strong survival signals, which you cannot block in any way.

SQ: How do you think you can prevent the development of drug-resistance?

TWM: By understanding mechanisms. For example, PTEN mutation leads to a signal for survival. Survival means the cancer cell is oblivious to chemotherapeutic agents and an enzyme called PKB mediates this process. If you block PKB, then you back up your cell survival signal and render the cell sensitive to chemotherapeutic agents. We hope to increase the therapeutic index. By doing so, the patients can tolerate a higher level of chemotherapy agents without first killing the patient.

In 1993, an affiliation was formed between Amgen Inc., an American pharmaceutical company, and the Ontario Cancer Centre. The company promised to spend 100 million Canadian dollars over the next ten years to create a medical research institute in Toronto that would study the immune system and its role in various diseases, such as cancer. Dr. Mak was chosen to be the Director of the Canadian Amgen Institute and he is also the Vice President of Research. The Amgen Institute represents an emerging type of partnership, in which specific areas of research carried out by an academic institute are funded by a private corporation in exchange for access to new research findings and rights of first refusal for all pending patents and inventions. As part of the affiliation agreement, the cancer centre retains some influence over the governance, recruitment, and review of procedures of the institute. However, the growing influence of private industry on academic research raises concern about how this might change the direction of research in the future.

TWM: It's a very sensitive issue. There are the die-hards who think that it is essential that we maintain academic freedom and not be influenced by the pharmaceutical industry in our medical research. The NIH budget in the States has just been released: 17.4 billion US dollars a year. In Canada, the MRC is about $300-400 million Canadian. We're talking about a 50-fold difference if not more. One to one, we cannot compete. And the days are mostly gone where somebody hides in the corner and thinks of such brilliant experiments that all he needs is a toothpick and a Q-tip. Today it's technology-driven research. It doesn't matter how smart you are. I beat people to understanding Hodgkin's Lymphoma, not because I was smart, but because I had technology that could look at thousands of genes at the same time, called DNA micro array chips. It's "leave no stones unturned" technology. Look at the Amgen Institute. We receive 85% of our funding from Amgen, but at the same time we maintain total academic freedom: we can publish, and all the mice that we made are distributed to all investigators with no strings attached. If we can make an alliance with the pharmaceutical companies that allows us to do that, but at the same time be able to have a pick on right of first refusal to our discovery, they have to be very convinced that there is a high likelihood that we will come up with something to make it worth their while. In a way, it's a lot of money, and in a way, it's a drop in the bucket for them. The NIH budget of 17.4 billion dollars is perhaps in the order of 3 or 4 pharmaceutical companies. Large pharmaceutical companies like Merck spend billions a year. A company like Merck spends about 10 times the whole of Canada. We cannot ignore that. We have to find a way of working with them. Of course, there will always be those that say that they will never shake their hands because they are the merchants of exploitation. The cost of drugs is very high.

SQ: Is it important to have people like you who have a foot in both worlds?

TWM: It's a very challenging job to walk that very fine line. It's been over six years since we've had this alliance with Amgen and although it has not been announced, it has been approved that they're going to give us another five years on top of the 10. Obviously, they are pleased with what we've done. We haven't delivered to them a drug that they could sell for five dollars, let alone a multi-billion dollar drug. At the same time, I would like to think that the institute has built a reputation of excellent research at the basic science level. I think we have walked that very fine line to create a win-win situation. It takes two to tango, but in this case it takes three: it's us in the middle, the pharmaceutical company on one side, and the academic community on the other side. We cannot be criticized

for having sold out and at the same time we have to make sure the pharmaceutical company knows that we also have their interests at heart. I think if you can do that, it sure beats writing ten grants.

SQ: Do you think this is a good way to prevent some of the talented scientists from leaving for the US?

TWM: I can tell you that right away. I think of the people that are here at this institute, I would be very surprised if half of them would stay in Canada if they didn't have this rather well funded situation. Look at Joseph Penninger: highly successful. At his age, there would be zero chance that he could run a lab in Canada and that he could finance himself at the level that he's doing right now. He's getting offered jobs everywhere; people throw millions of dollars at him. But he's still here. He's Austrian; he's from Europe; he has no loyalty. People *think* I'm stupid to stay here all of these years. But, it's also been said that "finally the mountain has come to Mohammed."

SQ: But it wasn't always like that. What made you initially resist going to the States?

TWM: Thirteen years ago when I was in my 30s, I was offered the position of Chairman of Pathology and Director of the Howard Hughes Institute at Yale. There was no comparison. Canada is a country that cannot afford to bid on a situation like that. At the end I knew that I made an excellent choice by staying because I could do everything that I wanted to do. It wasn't easy. I was writing grants every day until 3:00 a.m. I chose to stay because Canada is a great country. My children were growing up and they loved it here. My wife loved it here. I loved it here. I have everything I need to do successful research and Toronto is a very vibrant research community. If I had to do it over again, there is no question that I would stay.

SQ: It must be rewarding to know that it's something you helped build up on your own.

TWM: Yes, but I think that it's a lot more complicated than that. There's a sense that I'm too ambitious. Some people feel that I should be satisfied by doing my own thing instead of trying to build a bigger lab, for example, but I've got to live the life that I choose.

SQ: The medical field is very reliant on what is found from basic science research. Do you think it's important for physicians themselves to become involved in the world of research?

TWM: Absolutely. I have trained more physicians than I have non-physicians: the head of Haematology labs at Sunnybrook, the head of lymphoma at PMH, etc. In fact, by next year, I would say that 5 or 6 of the 8 graduate students that I have are either MDs or MD/PhD students and the vast majority of the post-doctoral fellows in my lab are MDs. These people are slightly different; they are Japanese and European MDs. They have traditionally a stronger tendency towards doing research. In Europe, a lot of the research is done by MDs who went into research after their medical school, whereas over here in North America, a lot of the basic research is done by PhDs and some MD/PhDs. MDs have a very different perspective. I do not believe in ivory towers. I believe that the whole purpose of my existence in this office is to drive medical research to the clinic. I'm not driving it at a level that is premature. If I have to build it from scratch, I will build that program from very basic science, but I will push it towards the clinic, as fast as I can. I certainly need all of the MDs that I can convince to come into my lab to make that push with me because the limit of my expertise will end at a point where they will take over. It's essential.

SQ: Do you need someone who can do both?

TWM: Of course I need someone who can do both because the one who is only doing clinical research will not understand half of what I say. I need someone who will understand all of what I say and be able to make that connection between what we have found and what is observed in the clinic. Having said that, it is a tremendously difficult job for a clinician-scientist to remain in the clinic, to be modern and up-to-date with all of the treatments, and at the same time, run a lab that is highly competitive. Basically clinician-scientists are competing against people who are working 100% of their time, when they can only work in research 70% of their time. So to some extent it's like a four-legged animal with one leg gone. For those who only work 50% of their time you can imagine a four-legged animal with only 2 legs. And I think for those who are only doing research 25% of their time, well, imagine that animal hopping along. It requires dedication. Sometimes it requires just picking a field where there is a niche that you can protect. But if you're interested in it, you have to get involved in it.

The best advice is often the most simple. Hence, in his usual style, Dr. Mak ends the interview with the following quote from John Greenleaf Whittier:

TWM: You only live once. Of all said words of tongue and pen, the saddest are "it might have been."

The Sixth Canadian Conference on International Health: Shifting Global Environments for Health and Development

Hull, Quebec, November 14 – 17, 1999

Tara Kiran, B.Sc. (0T2)

Introduction

Every year, more than 300 professionals from around the world gather in Ottawa-Hull for the Canadian Conference on International Health. Participants are encouraged to challenge current concepts in international health, network with experts in the field, share their most recent research findings, and discuss the latest Canadian field-based activities. The conference features high-profile keynote speakers, over 30 different symposia, more than 15 exhibits and at least 20 poster presentations. The topics of discussion range from malnutrition and HIV/AIDS to health policy and globalization. The following article summarizes two of the most interesting topics presented at the sixth annual conference.

Global Public Health

Professor Ilona Kickbusch, Director of the Division of International Health at Yale University, opened the conference by challenging participants to view public health in a global context. She argued that health should be viewed as an investment shared by the global community and not simply as the well-being of an individual. A healthy population contributes labour, ideas, and values to global society. Furthermore, health is not just the absence of medical illness but must include the assurance of basic human rights and equity.

Once health is seen as a "global public good," it becomes clear that we need health policy that transcends national boundaries. A global convention on tobacco control, for example, is the first step towards such global action. Every country has a stake in the health status of a population abroad. International development assistance can thus be recast as globalized internal policy.

It also follows that the public health policy of one nation can have an international impact. Governments may inadvertently be endangering the health of those abroad by failing to deal adequately with a public health issue at a domestic level. For example, the failure to appropriately treat and manage tuberculosis patients could lead to the spread of multi-drug resistant tuberculosis across international boundaries. More complex sequelae may result from a government's failure to recognize basic human rights.

Health policy, therefore, must be globally accountable because the actions of any one nation may have international repercussions. However, when is it appropriate to take action to promote global health? When can the global community intervene to counter gross health abuses? Would our actions differ if we were dealing with human rights abuses? These are hinge questions requiring international dialogue before answers can be found. At present, Kickbusch argues, the support base for global health must extend. There is a need for improved communication and coordination between international agencies promoting health. The World Health Organization must take on the role of defining global public health challenges. Ultimately, we must look towards creating a suitable global health infrastructure.

Managing Ecosystems for Human Health

Throughout the conference, the International Development Research Centre (IDRC) and the United

Nations Environmental Program (UNEP) ran a consultation entitled Ecosystem Disruption and Human Health. Their aim was to test the hypothesis that better management of ecosystems results in improved human health.

Don Peden, a Senior Program Specialist of the IDRC opened the consultation with an overview of the interaction between ecosystems and human health. An ecosystem is defined as a dynamic complex of plant and animal communities within an artificial geographical boundary that includes both the living and non-living environments. An ecosystem can have both positive and negative impacts on human health. On the one hand, it can provide food, security, and an habitual climate. On the other hand, it can also provide a habitat for disease vectors or contain naturally occurring toxins. Likewise, human health can have a positive or negative impact on an ecosystem: endemic malaria reduces settlement of a geographical area, thereby decreasing the stress on the natural environment that can accompany human settlement; the HIV/AIDS epidemic in Uganda has resulted in lost labour, altered farming practices, decreased soil fertility, and a decrease in the variety of crops grown. Ongoing research is striving to understand the complexities of the interactions between human health and ecosystems.

The conference provided an excellent opportunity to learn about the IDRC's Ecosystems Approaches to Human Health Program Initiative. The Initiative's goal is to improve human health by supporting trans-disciplinary research on the structure and function of stressed ecosystems. It focuses on three specific systems: mining, agriculture, and the city. The Initiative's research incorporates three methodological approaches. (1) The *trans-disciplinary* approach allows researchers to see the same situation from different perspectives. Teams could include a medical doctor, engineer, environmental scientist, biogeochemist and social scientist. Researchers would consider everything from the health, economic status, and culture of the population to the pollution of the surrounding environment. (2) *Community participation* is also a key aspect of the Initiative's research. It helps researchers understand how to overcome stakeholder disagreement and helps ensure the development of an effective policy. Finally, (3) all research protocols are *sensitive to social variables* such as class, caste, ethnicity, and gender. This approach recognizes that environmental stressors can have varying impacts on different groups. In particular, sensitivity to social variables allows for the identification of vulnerable groups. Overall, the IDRC's initiative aims to place human health in its broader ecological context.

The highlight of the IDRC/UNEP consultation was David Suzuki's keynote address on "the ecological millennium." According to Suzuki, current consumption patterns and societal behaviours disrupt our ecosystem and thus undermine the sustainability of human communities. Government and industry have economic priorities. As a result, they ignore the direct impact we have on our ecological community as well as the indirect impact we have on our biological, social, and spiritual needs. Suzuki argued that "the ecological millenium" will demand significant changes in our consumption patterns, ethics, behaviours, and attitudes. We must begin to see ourselves as part of the global environment. In this light, the move towards an ecosystem approach to human health, an approach that demands increased appreciation for the complex interactions between ecosystems and human health that affect the sustainability of both, makes perfect sense.

Conclusion

The conference proceedings suggest a paradigm shift from international to global health. Our health is influenced by the state of our ecosystem, including the well-being of other human populations. We will need to understand how we interact with our global environment to manage human health effectively in the twenty-first century.

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Commentary

Clinician-Scientists Accountable to Disparate Institutions: Hospital, University, and Industry

Martin C. Chang, Ph.D. (0T3) and Maria F. Muraca, M.Sc. (0T3)

In the wake of recent events at the Hospital for Sick Children (HSC), questions are being raised about the reputations of prominent researchers and about the hospital administration itself. To an outsider, a bewildering picture, full of lurid intrigue, is painted by the popular media. From the pushing of experimental drugs to broken contracts, from conspicuous silence on the part of the hospital administration to a shocking barrage of hate-mail, the controversy seems to reflect an unusual breakdown in the hospital organization. In reality, the underlying conflicts that have come to light are neither unusual nor do they result from a lack of organization. Rather, they reflect a fundamental problem in how clinical research is organized around disparate institutions.

While even the earliest physicians tried to apply a scientific (or at least systematic) approach to the treatment of disease, the information explosion of the late 20th century has resulted in a new type of "clinician-scientist." The last two decades have seen a rapid growth in clinical research carried out by physicians under the auspices of various institutions and the enthusiastic adoption of bench-to-bedside approaches. Along with new research activities, however, come new responsibilities and challenges. In particular, the clinician-scientist constantly shifts between three main institutional settings: the hospital/clinic, the university, and private industry. Although all three institutions share the desire for improved health and health care for patients, each have their own immediate motives. When these priorities are at odds, professional conflicts may arise for the clinician-scientist, who is potentially accountable to all three institutions.

Hospitals mainly provide acute patient care in the community. As part of their mandate to serve community health interests, hospitals may participate in a number of academic programs, including medical education and research. Research institutes within hospitals, however, are usually segregated administrative bodies peripheral to the everyday operation of the hospital as a whole. As a result, demands for patient-care resources within the hospital often supersede demands for laboratory resources. Although hospitals do raise funds to support their research institutes, each investigator is generally expected to provide funding from external sources: funds are most commonly secured from federal agencies, although contributions from private industry are becoming more and more significant.

Universities are similar to hospital research institutes in that they provide resources to build an academic community except that, in the case of the university, academic interests are central and not peripheral. The priority of a university is to provide an environment of intellectual freedom and communication such that knowledge can flourish. In principle, by working within the academic setting, the intellectual rights and opportunities of the scientist are protected and expanded. Ideas that may otherwise encounter neglect or resistance from the pressures of public opinion or industrial lobbies are given full (if not always unbiased) consideration in an academic forum. As a result, the clinician-scientist must not only consider the needs of the hospital, but also has a responsibility to participate fully as a member of an academic community through teaching, publication, and various peer review processes.

the contributions of private industry have profoundly impacted clinical research in both hospital and university settings. On the one hand, the infusion of funds from the marketplace gives the research sector added vitality and competitiveness. On the other, it has imposed the effect of market forces on patient care and academic freedom. Private funds come from companies as short-term investments. Some companies have a marketable idea that requires technological advances in other areas to make viable. Many drug companies are looking for a clinical testing range for their pre-designed compounds. Still others are looking to invest in a "brain mine" that they can pick at without laying down their own research-and-development infrastructure.

In cases where substantial amounts of private money drive research activities, the priorities of hospitals and universities become influenced by the short-term agendas of the private companies. For example, when a company makes a large donation to a hospital research institute, it rarely benefits the entire hospital. Such donations are often earmarked for certain high-profile or marketable ventures, and they compel the hospital research administration to bias its infrastructure priorities in favour of prevailing market forces. This will inevitably have a significant impact on a clinician-scientist who relies both on the physical environment provided by a hospital or university, and on private funding.

By considering, therefore, the conflicting roles of a clinician-scientist, one can begin to decipher the chain of events surrounding the HSC controversy. The conflicts in this particular case began when a generic drug manufacturer, Apotex, Inc., funded a set of trials to evaluate a new oral iron-chelation treatment for thalassemia patients. This study was led by a clinician-scientist, Nancy Olivieri, who upon discovering data revealing harmful effects of the drug, breached a confidentiality contract. This led to an open conflict between Dr. Olivieri, who was concerned for the well-being of patients participating in the study, and Apotex, who was in a legal position to seek damages. The conflict was further complicated by the mixed reaction on the part of HSC and the University of Toronto. Although, in principle, a hospital must place patient welfare first, and a university must support academic freedom, substantial funds were promised to both institutions by Apotex, in conjunction with this and other projects. These private interests seem to have led to an unwillingness to side against the company.

In the subsequent deterioration of confidence in the HSC research institute's ability to provide a supportive research environment, several prominent investigators have resigned their high-profile posts in HSC to take up positions at other hospitals. Dr. Gideon Koren, a highly regarded scientist and clinician, who had disagreed from an early stage with the findings of his colleague, Dr. Olivieri, chose a less constructive way of expressing his frustration with the growing environment of conflict. After being identified as the author of several angry, anonymous "poison pen" letters sent to Dr. Olivieri and several other HSC staff members in late 1999, he has been forced to resign. Given Dr. Koren's senior positions in both the hospital and university, and his various collaborations with private interests, one may speculate that he perceived himself to be a focal point for the conflicts prevailing at HSC, and that he acted out of fear or frustration. However inexcusable Dr. Koren's actions may be, his motivation in taking this action can be traced to the disparate forces tugging at all clinician-scientists. There is a need on the part of our public and private institutions to address these potential conflicts actively.

Recognizing that hospitals, universities, and private corporations will always have their own priorities, a number of principles must be clarified to improve the working environment of a clinician-scientist. Within the hospital, the important link between research and health must be better recognized, both in the administration of research institutes within the hospital organization, and in the public promotion of hospital research activities. Within the university, the complete and honest publication of data must be given unequivocal support, regardless of potential political controversies or monetary losses. In the private sector, more donations to health care and universities must be given unconditionally, for the global long-term good, and not as earmarked investments. Companies requiring a clinical setting to advance their products must recognize the immediate duties of those responsible for clinical care. Ultimately, each individual clinician-scientist may work under three roofs, but they will all work for their patients: at the bench to ensure that the most advanced care options are available, and at the bedside to provide compassionate care.

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Law and Ethics in Medicine

Series Editor, Anna A. Kulidjian, M.Sc. (0T2)

Informed Consent in the Clinical Setting

Fayez A. Quereshy, B.ArtsSc. (0T3) and Hemant A. Shah, B.ArtsSc. (0T3)

Law and Ethics in Medicine
This series is intended to serve as an introduction to legal and ethical issues in medicine. It will feature articles from experts in the field, as well as from medical students and trainees. The goal of this series is to clarify important legal and ethical issues before they become concerns at the bedside. Please direct any comments, questions, or suggestions regarding this column to the Series Editor, Law and Ethics in Medicine at the following e-mail address: editors.utmj@utoronto.ca.

Abstract
Health care provision in Ontario has undergone a paradigm shift, from the paternalistic notion of patient care to that of informed consent and patient autonomy. The concept of informed consent has been developed through both common law cases and legislation and is now defined as the delivery of material information of a quality that allows the patient to make an autonomous decision. There are, however, exceptions to the rule of informed consent. The onus for proving that an exceptional situation exists is the responsibility of the physician. Thus, in the clinical setting, great care must be given to informed consent in order to avoid complaints and litigation. More central to the philosophy of informed consent is that it acts as the impetus for patient-physician dialogue, and as a trustee for high quality patient care.

Introduction
Provision of Health Care in Ontario is underscored by a complex set of changing ethical and legal responsibilities. As expressed in the Hippocratic Oath, "I swear by Apollo and Aesculapius [that] I will follow that system of regimen which according to *my* ability and judgement *I* consider for the benefit of *my* patients."[1] This paternalistic notion of the patient-physician relationship is no longer reflected in modern medicine; Mill's concept of patient autonomy is a more prominent influence on clinical practice today. This paradigm shift forces physicians to face the medico-legal challenge of obtaining informed consent.

Defining informed consent is marred by its colloquial usage. Incorrectly, physicians and others assume that treatment refusal by patients implies they are not adequately informed.[2] As such, informed consent has become a process for convincing the patient to undergo a clinical procedure. Unfortunately, this approach confines the physicians' role to providing information, and the patients' role to consenting.

Informed consent is the provision of information of a quality such that it allows the patient to make an autonomous decision. Implicit in this definition is that consent is voluntary, and is obtained from a competent individual.[3] Moreover, it suggests a consultative process that involves dialogue between doctor and patient.

History

Now entrenched in both case and common law, the legal concept of informed consent took nearly a century to define. In the case of *Schloendorff v. The Society of New York Hospital* in 1914, Justice Cardozo stated that, "Every human being of adult years and sound mind has a right to determine what shall be done with his own body; and a surgeon who performs an operation without his patient's consent, commits an assault."[4] This U.S. case laid the groundwork for the concept of consent. The term informed consent first appeared in courts in 1957 in the case of *Salgo v. Leland Stanford Jr. University Board of Trustees*. The patient, Salgo, suffered paralysis as a result of aortography. The presiding Justice ruled that, "In discussing the element of risk a certain amount of discretion must be employed consistent with the full disclosure of facts necessary to an informed consent."[5] These American cases formed a foundation for Canadian jurisprudence.

Canadian doctrine is largely based upon the 1980 Supreme Court of Canada judgements in *Hopp v. Lepp* and *Reibl v. Hughes*. These cases transferred the liability associated with informed consent from assault and battery (non-consensual touching) into the boundaries of negligence, and more importantly, helped to define the standards of disclosure.[6]

Where We Are Today

Currently in Ontario, the *Health Care Consent Act of 1996* stipulates that, "A consent to treatment is informed if, before giving it . . . the person received the information about the matters set out in (Table 1) that a reasonable person in the same circumstances would require in order to make a decision about the treatment."[7] While this requires the physician to treat his/her patient as a reasonable person in law, the Supreme Court of Canada adds an additional caveat: the physician must go beyond an objective standard, and provide limited context specific information.[8,9]

Patient expectation of informed consent is often inconsistent with that of the practitioner, prompting complaints and litigation.[10] It is widely accepted that informed consent can be written or oral. However, it is often forgotten that it also must be periodically renewed and is subject to change. These characteristics of informed consent were solidified in *Nightingale v. Kaplovitch*, where the patient's request for cessation of a sigmoidoscopy was ignored by the gastroenterologist. The plaintiff was awarded damages for the physician's negligence. Thus, obtaining informed consent does not bind a patient to accept treatment, but simply insures that no treatment is performed without agreement.[11] Hence, informed consent is a mechanism to improve communication between physician and patient throughout the therapeutic relationship.

Table 1
Disclosure Requirements of Informed Consent[22]

1. The nature of the treatment.
2. The expected benefits of the treatment.
3. The material risks of the treatment.
4. The material side effects of the treatment.
5. Alternative courses of action.
6. The likely consequences of not having the treatment.

Exceptions

Though informed consent should be obtained whenever possible, there are accepted situations in which the requirements, by law, do not apply. These exceptional situations include waiver by the patient, emergencies, and therapeutic privilege.[12]

When faced with either a written or oral waiver by a patient, a physician must always be conscious of associated contextual issues; that is, why does the patient not wish to be informed? In this scenario, ethno-cultural and socio-economic factors should be considered. A waiver, however, does not absolve a patient of active participation in his/her treatment.

In emergency situations, the requirements for informed consent are less stringent. Indeed, if the patient is in imminent risk of serious injury then a practitioner may proceed without explicit approval.[13,14] However, a stipulation exists: the patient's expressed opinions when competent must always be respected.

Therapeutic privilege involves a physician withholding or generalizing information he/she believes would be counter-therapeutic for a specific patient. "A physician's privilege to withhold information for therapeutic reasons must be carefully circumscribed, however, for otherwise it might devour the disclosure rule itself."[15] As such, the legal framework for invoking therapeutic privilege places a strong burden of proof on the physician to demonstrate a benefit.

Case Studies

Case 1

Mary Dalton, a 27-year old G1P0 woman at term, began active labour three hours ago. Her initial phase of labour is unremarkable. The obstetrician on call is summoned due to complications with the delivery; he finds that the fetal heart rate is at 55 beats/min. After using conservative labour

measures for three minutes, such as maternal positioning, maternal oxygen and increased intravenous fluids, there is still no response. The attending nurse states that Mary is 4 to 5 cm dilated and there is no cord prolapse. The obstetrician explains to Mary that an emergency Caesarean section may be needed if there is severe fetal distress. Mary responds, "I do not want a Caesarean!"[16]

Does Mary have the Right to Refuse Treatment even though it may Result in Severe Harm or Death to the Fetus?

From a legal perspective, Mary does have the right to refuse the C-section provided that she is deemed competent, that the decision is voluntary, and that she is well informed.

How is Mary's Competency Assessed?

An otherwise competent individual may be dubbed incapacitated in an acute scenario. The physician must therefore consider whether or not certain prevailing conditions exist. If the patient shows evidence of confused or delusional thinking, possibly precipitated by medication, then the physician is obligated to assess the degree of incompetence. Further, if the patient is experiencing severe pain, acute fear or anxiety, the validity of his/her decision making is suspect. In the case of Mary's refusal, the obstetrician may decide that she was, in fact, incapacitated by anaesthetics, pain, or fear of surgery. However, to invoke this therapeutic privilege, the burden of proof rests with the physician to demonstrate that exceptional circumstances existed. The physician must also determine if the decision is well informed. Mary's refusal of treatment may be attributed to her lack of understanding of the procedures and/or the associated risks. The physician is obligated to educate his patient directly or arrange for such education.

Does the Fetus have any Rights?

The correct legal answer is no. According to the law, the fetus is not considered to be a person until birth. As such, the maternal right to autonomy prevails. Morally, however, this situation presents an interesting dilemma: knowing that the fetus' status changes upon birth, should the physician consider its best interests as well? Perhaps the most appropriate action for the physician is to ensure that the mother is fully aware of the consequences of her decision on the fetus' welfare.

What is the Physician's Responsibility?

The physician's responsibility is not to convince the patient to accept treatment. Rather, he/she should clarify the terms of the refusal, assess competency, and continue to care for that patient as necessary.

Case 2

Jimmy Quinn, a 15 year-old boy with classic cystic fibrosis, is brought into the hospital by his parents. Jimmy's father complains that over the last three weeks Jimmy has refused to take an active role in his own therapy. Jimmy asserts that his chronic condition has taken an emotional toll. Jimmy's parents ask the physician at the clinic, whom they have been seeing for four years, to force Jimmy to comply. The physician recalls noting in Jimmy's chart that he is a well-adjusted, mature, young adult. During their meeting, the physician outlines the consequences of Jimmy's ambivalence. Jimmy listens, then retorts, "I can't take it anymore. Just let me die."

Can Jimmy Refuse Treatment?

The legal answer is yes. While it is a societal norm that parents make health care decisions for their children, the age of maturity or competency is not defined in common law cases or legislation. As a result, the physician must assess the child's ability to rationally think and deliver informed decisions. In this particular scenario, it is clear that Jimmy is the most familiar with the circumstances of his condition. In child decision making, two fundamental principles underpin health care provision: "these are the promotion of children's well being and opportunities to flourish, and help for children to become empowered."[17] Allowing Jimmy to choose his course of treatment permits his empowerment, but challenges his personal well being. However, this concept of well being remains elusive; though his life may be shortened by his decision, its quality may be enhanced. This discussion highlights the importance of perspective in determining the degree of well being. It should be maintained that the physician's primary concern deals not with the consequences of a decision, but rather if that decision was made by an informed and able patient.

What are the Legal Parameters of Substitute Decision Making for Children?

While the discussion surrounding proxy decision makers is exhaustive, this paper will summarize a few salient points. Firstly, who may make a decision on behalf of a child? If the child is incapable, then the parents or legal guardian(s) may make the decision to either accept or refuse treatment provided they are capable, not prohibited by court order, and are willing to assume the responsibility.[18] Secondly, what are the standards to which the substitute decision maker is held? The *Health Care Consent Act* directs the substitute decision maker to consider whether the treatment is likely to improve the child's condition or well being, or prevent it from deteriorating. Moreover, they are directed to reflect on the weighted benefits and risks associated with or without treatment. Finally, there is an onus on the proxy to evaluate whether a less restrictive or intrusive method of treatment would be equally beneficial.[19]

Case 3

Ryan James, a 53 year-old machinist, has suffered from an indirect inguinal hernia. He consents to a routine corrective operation at the local hospital. During the procedure, the surgeon finds that one of Ryan's testicles is diseased and potentially gangrenous, threatening the patient's health and/or life. While the patient was under general anaesthetic, the testicle was removed even though the patient could not be informed, nor could consent be obtained. The patient later sued the surgeon.[20]

Can a Physician Operate Without Consent?

As outlined above, specific circumstances arise in which a physician can act without consent. In this example, the surgeon was responding to a perceived emergency. This case can be compared with traditional emergencies in which incapacitated patients 'arrive at the hospital door.' In both scenarios, the fundamental tenet is the same: the patient's life is in danger. In fact, the courts have maintained that, "where a great emergency which could not be anticipated arises . . . it is the surgeon's duty to act in order to save the life or preserve the health of the patient, and . . . in honest execution of that duty he should not be exposed to legal liability."[21] Thus, in this scenario, the patient would not have been successful in his suit.

Conclusion

While informed consent has been explored in medico-legal literature for many years, several issues still remain unresolved. For example, the emerging field of clinical genetics presents new challenges: can a physician ever adequately inform his/her patients about the consequences, including social and economic, of a positive test on a screen? As common law cases have explicitly outlined the roles and responsibilities of physicians with regards to informed consent, the moral and emotional elements associated with patient-centred care are often ignored. Although a physician is obligated to respect a patient's wishes, one must also remember that physicians are vulnerable to human emotion. Ironically, it is this emotion that brings the physician closest to the patient in the clinical environment, but also obscures the issue of informed consent.

References

1. As quoted in: Katz J. (1998). Reflections on informed consent: 40 years after its birth. *J Am Coll Surg.* 186: 469.
2. Dickens BM. (1999). Informed consent. *In: Canadian Health Law and Policy.* Downie J and Caulfield T (ed). Butterworths: Markham, pp. 117-141.
3. Nelson E. (1999). The fundamentals of consent. *In: Canadian Health Law and Policy.* Downie J and Caulfield T (ed). Butterworths: Markham, pp. 101-116.
4. As quoted in: Katz J. (1998). Reflections on informed consent: 40 years after its birth. *J Am Coll Surg.* 186: 466.
5. As quoted in: Katz J. (1998). Reflections on informed consent: 40 years after its birth. *J Am Coll Surg.* 186: 466.
6. Dickens BM. (1999). Informed Consent. *In: Canadian Health Law and Policy.* Downie J and Caulfield T (ed). Butterworths: Markham, pp. 117-141.
7. Ontario Health Care Consent Act 1996, Chapter 2, Schedule A, Section 11(2) and 11(3). Accessible from http://209.195.107.57/en/index.html
8. Dickens refers to this as a modified objective standard.
9. Dickens BM. (1999). Informed consent. *In: Canadian Health Law and Policy.* Downie J and Caulfield T (ed). Butterworths: Markham, pp. 117-141.
10. McIlwain JC. (1999). Clinical risk management: principles of consent and patient information. *Clin Otolaryngol.* 24: 255-261.
11. Nelson E. (1999). The fundamentals of consent. *In: Canadian Health Law and Policy.* Downie J and Caulfield T (ed). Butterworths: Markham, pp. 101-116.
12. Hebert PC. (1996). *Doing right: A Practical Guide to Ethics for Physicians and Medical Trainees.* Oxford University Press: Toronto.
13. Hebert PC. (1996). *Doing right: A Practical Guide to Ethics for Physicians and Medical Trainees.* Oxford University Press: Toronto.
14. The legal approach is that peril invites rescue, and that a person in peril is taken to give implied consent to reasonable rescue efforts, including intervention.
15. Dickens BM. (1999). Informed consent. *In: Canadian Health Law and Policy.* Downie J and Caulfield T (ed). Butterworths: Markham, p. 137.
16. This case is adapted from: Flager EA in association with RCPSC Biomedical Ethics Committee. (1999). Bioethics for clinicians: Obstetrics and gynecology. *Annals of the RCPSC.* 32 Supp: 23-42.
17. Rowell M and Zlotkin S. (1997). The ethical boundaries of drug research in pediatrics. *New Frontiers in Ped Drug Ther.* 44: 27-39.
18. Ontario Health Care Consent Act 1996, Chapter 2, Schedule A, Section 20(1). Accessible from http://209.195.107.57/en/index.html
19. Ontario Health Care Consent Act 1996, Chapter 2, Schedule A, Section 21(2c). Accessible from http://209.195.107.57/en/index.html
20. This case is adapted from Marshall v. Curry found in: Nelson E. (1999). The fundamentals of consent. *In: Canadian Health Law and Policy.* Downie J and Caulfield T (ed). Butterworths: Markham, pp. 101-116.
21. As quoted in: Nelson E. (1999). The fundamentals of consent. *In: Canadian Health Law and Policy.* Downie J and Caulfield T (ed). Butterworths: Markham, p. 105.
22. Ontario Health Care Consent Act 1996, Chapter 2, Schedule A, Section 11(3). Accessible from http://209.195.107.57/en/index.html

ROSS MEMORIAL HOSPITAL

The Health Services Restructuring Commission has directed that Ross Memorial Hospital will play a strengthened role in the delivery of health care in Victoria County and the surrounding area, promoting the expansion and enhancement of services.

Positions are available immediately in Family Medicine and Emergency Medicine, and opportunities exist in some specialty areas. The hospital has 155 beds to be increased to 218 by 2003.

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Law and Ethics in Medicine

HIV Testing in Pregnant Women: Ethical Considerations

Elizabeth Gold, B.Sc. (OT2)

The global HIV/AIDS pandemic is continuing unabated and the number of people living with HIV/AIDS worldwide has tripled in the last decade. Most of the estimated thirty-five million people infected with HIV live in developing countries. In North America the number of new HIV infections in women is now growing at a faster rate than that of men. Canadian epidemiological data shows that women comprised 21.5% of HIV-positive test results in 1996, more than double the number between 1985-1994.[1] AIDS is now one of the leading causes of death in all women aged 25 to 44 years in the United States.[2] The virus has a long latency period and thus most of these women were infected during adolescence or in their early twenties. In Canada women make up less than 10% of the total number of AIDS cases, but the majority of these cases are in women of reproductive age (15-44).[3] Much of the recent attention given to HIV infection in women has focused on maternal to child (vertical) transmission. This article discusses some of the historical, ethical, and legal considerations of HIV testing during pregnancy in Canada.

Reported rates of vertical transmission in the absence of preventative measures range from 15-40%.[4] Transmission can occur *in utero,* during labour and delivery, or through breast milk. Interventions to reduce vertical transmission were first demonstrated in the AIDS Clinical Trial Group Study 076. This study compared vertical transmission rates between HIV positive women receiving zidovudine or placebo. This study was interrupted in 1994 when it revealed a significantly lower transmission rate in the treatment group and it was felt to be unethical to continue giving HIV positive women placebo. The final results were vertical transmission rates of 8.3% in the zidovudine group versus 25.5% in the placebo group.[5] Subsequent studies have demonstrated that vertical transmission rates can be even further reduced when zidovudine is combined with HAART (highly active antiretroviral therapy), the current standard of care in treatment of HIV infection.[6] The potential long-term effects of exposure to these drugs during pregnancy are unknown and there can be significant limitations in adhering to antiretroviral therapy.[7] The guidelines regarding treatment of HIV/AIDS and interventions to reduce vertical transmission are continually being reevaluated and updated.

The goal of counselling about and testing for HIV infection in pregnant women should be to provide infected women with support, access to appropriate treatment, and information to decrease the risk of HIV transmission to their children and sexual partners. Samson and King state that, "early diagnosis of HIV infection in a pregnant woman optimizes her medical and psychosocial care, decreases the incidence of mother-to-child transmission and decreases the risk of horizontal transmission to sexual partners."[8] Counselling is also seen as an important component of primary prevention, as it is an opportunity to provide uninfected women with information that may help them remain HIV negative.

Since HIV testing became available in the 1980s there has been agreement among health care providers and policy makers that people should be tested only with their informed, voluntary, and specific consent. The main reason for this approach is that there is significant stigmatization of and discrimination against people living with HIV/AIDS.[9] Counselling is required both before and after HIV testing and is a part of informed decision making.[10] Specific consent means, for example, that the blanket consent to testing and treatment forms that patients sign when admitted to hospital do not include HIV testing. Before a testing policy is implemented, models of care for HIV positive individuals and families should already be in place.

There are several possible types of prenatal HIV testing programs: mandatory, voluntary, targeted, and universal. HIV testing is not currently mandatory under any circumstance in Canada, although it is required in a few specific circumstances such as if a person chooses to donate blood or organs.[11] A theoretical benefit to a mandatory prenatal testing program would be that it would have the potential to identify all HIV positive women who present for prenatal care. However, most studies have concluded that the harms of mandatory testing outweigh the benefits. Mandatory programs that would force women to undergo an HIV test as a prerequisite to obtaining medical care could have detrimental effects on both maternal and child health. Some women would be discouraged from seeking any prenatal care.[12] This would counter the ethical principle of beneficence, as it would do more harm than good. Coercive testing without voluntary informed consent also contradicts the principle of autonomy. The principle of autonomy is central to any discussion of medical ethics, since it means that competent individuals have a near absolute right to make their own health care decisions.[13]

Mandatory HIV testing is difficult to defend legally as well as ethically. Canadian case law enshrines the right of patients to give or refuse consent to medical testing and treatment. The Supreme Court has ruled that the right of a woman to give or refuse informed consent is not restricted by pregnancy.[14] Finally, any legislation that allowed the government to force a pregnant woman to undergo an HIV test would likely contravene the *Canadian Charter of Rights and Freedoms*. In contrast, voluntary testing respects both the ethical principle of autonomy and the legal rights of women.

Initial HIV testing programs for pregnant women specifically sought to test only women with identifiable risk factors (targeted testing). The problem with this approach was that many women were unaware of or unwilling to disclose their own or their partners risk behavior. Physicians also failed to identify many women at risk.[15] Women who were infected through sexual contact with men or who had no identifiable risk factors comprise the majority of AIDS cases in Canadian women.[16] Thus, there has been an increasing shift to universal testing policies, which advocate offering HIV testing to all pregnant women. Universal and voluntary programs ensure that HIV counselling is provided to all pregnant women and all of these women are then offered an HIV test. The voluntary component means that after receiving counselling, a woman has the right to refuse to consent to an HIV test. Well-designed and implemented universal and voluntary strategies can be effective in increasing the uptake rates of prenatal HIV testing.[17] However, some urban centres with universal and voluntary programs have had less success, especially where women felt that services were lacking confidentiality and cultural sensitivity.[18,19] Lower levels of uptake may also result from the fact that not all physicians counsel pregnant women about HIV. Women may also choose to have an HIV test at an anonymous test site and not disclose this to their physician. In order to increase the effectiveness of prenatal HIV testing policies, women themselves need to have greater input into their development and evaluation.[20]

The wording of the official policy of the Ontario Ministry of Health has recently been changed from "HIV testing *should be discussed* with all pregnant women and all women considering pregnancy" to "HIV testing *must be offered* to all pregnant women and all women considering pregnancy."[21] This new universal prenatal counselling and voluntary HIV testing policy explicitly states that informed consent, as well as pre- and post-test counselling is required. Inherent in the provision of counselling is the fact that women have the right to refuse HIV testing and even to refuse recommended treatment. The ethical principles of justice and beneficence dictate that quality of care should not be affected by a woman's decisions regarding testing.[22]

Physicians who fail to inform women about the risks of HIV during pregnancy and who fail to offer HIV testing to pregnant women would be vulnerable to a civil suit by the woman and to professional misconduct charges by the College of Physicians and Surgeons. Conversely, a physician who performed an HIV test on a woman without meeting the requirements of informed consent could also face significant legal consequences.[23]

In conclusion, physicians have a legal and an ethical obligation to provide counselling on HIV related concerns to all pregnant women, and ideally to all women. Women have the right to receive linguistically and culturally appropriate HIV counselling. They have the right to have access to voluntary HIV testing, treatment, and appropriate HIV care. Hopefully, the medical care of all women will one day meet these standards.

References

1. Division of HIV/AIDS Epidemiology, Bureau of Communicable Disease Epidemiology, Laboratory Centre for Disease Control, Health Canada. (1996). *Inventory of HIV incidence/prevalence studies in Canada.* Health Canada: Ottawa.
2. Fowler, MG, Melnick SL and Mathieson BJ. (1997). Women and HIV: Epidemiology and global overview. *Obstet Gynecol Clin N A.* 24: 705-729.
3. Samson L and King S. (1998). Evidence-based guidelines for universal counselling and offering of HIV testing in pregnancy in Canada. *CMAJ.* 158:1449-1457.
4. McIntyre J. (1999). HIV in Pregnancy: A Review. WHO & UNAIDS: New York.
5. Sperling RS, Shapiro DE, Coombs RW, *et al.* (1996). Maternal viral load, zidovudine treatment, and the risk of transmission of human immunodeficiency virus type 1 from mother to infant. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. *NEJM.* 335: 1621-1629.
6. International Perinatal HIV Group. (1999). Conference Record, 12th World AIDS Conference, Geneva.
7. Public Health Service Task Force. (1998). Recommendations for the use of antiretroviral drugs in pregnant women infected with HIV-1 for maternal health and for reducing perinatal HIV-1 transmission in the United States. *Morbidity & Mortality Weekly Report.* 47(RR-2).
8. Ibid at 3, p. 1451.
9. Jurgens R. (1998). HIV Testing & Confidentiality: Final Report. Canadian HIV/AIDS Legal Network & Canadian AIDS Society.
10. For a more complete discussion of the components of HIV counselling see Canadian Medical Association, Expert Working Group on HIV Testing. (1995). Counselling Guidelines for HIV Testing.
11. Canadian Medical Association, Expert Working Group on HIV Testing. (1995). Counselling Guidelines for HIV Testing.
12. Nakchbandi IA Inaam A, Longnecker JC, *et al.* (1998). A decision analysis of mandatory compared with voluntary HIV testing in pregnant women. *Ann Intern Med.* 128:760-767.
13. Post N. (2000). Ethics in pediatric care. *In: Nelson Textbook of Pediatrics.* Behrman RE, Kliegman RM and Jenson HB (eds). WB Saunders: Philadelphia.
14. Supreme Court of Canada. (1997). Winnipeg Child and Family Services (Northwest Area) v DFG, 3 SCR 925.
15. Cooper EB. (1997). HIV disease in pregnancy: ethics, law and policy. *Obstet Gynecol Clin N.* 1. 24:899-910.
16. Health Canada. (1996). AIDS in Canada: Annual Report on AIDS in Canada. Division of AIDS Surveillance, Bureau of HIV/AIDS and STD, Laboratory Centre for Disease Control.
17. Ibid in 9.
18. Duffy TA, Wolfe DA, Varden C, *et al.* (1998). Antenatal HIV testing: current problems, future solutions. Survey of uptake in one London hospital. I. .316:270-271.
19. Goodman M. (1998). Reducing the vertical transmission of HIV: Women must be consulted. *BMJ.* 316:1900.
20. Boyd FM, Simpson WM, Hart JG *et al.* (1999). What do pregnant women think of the HIV test? A qualitative study. *AIDS Care.* 11:21 29.
21. Ibid in 9, p.138.
22. Ibid in15.
23. Ibid in 9.

Back to Basics II

An Approach to the Chest X-Ray

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This is the second instalment of a three-part series in which essential diagnostic tests of key importance in medicine are reviewed.

Introduction

The chest x-ray is a valuable tool in the diagnosis of respiratory and cardiac disorders. It also enjoys widespread use in emergency medicine and can detect systemic diseases such as metabolic bone disease and pulmonary metastases. The key to reading a chest film is to take a systematic approach. In this second instalment of the Back to Basics series, a methodical approach to the chest film, as well as some common disorders presenting with lesions identifiable on the chest x-ray, will be discussed.

The reader should note that the aim of this article is neither to present a comprehensive listing of all possible chest radiograph abnormalities nor to discuss the etiologies of these abnormalities. However, a great variety of subtle and obvious abnormalities, which may represent an underlying disease process, are identifiable using a systematic method as described below.

Background Information

X-rays are high-energy photons that penetrate matter to an extent that depends generally on the density of the substance. Gases are least dense. Soft tissues including all solid organs are of intermediate density, while bones and other calcium-containing structures are the most dense. Plain x-ray films are produced by passing x-rays through the body and onto a film. There is an intervening cassette which converts the x-ray energy into light; the light so produced creates an image on the film. Intervening matter attenuates the x-rays to a variable extent, with the result that areas of the film underlying dense structures are exposed to a lesser degree than areas of the film underlying less dense structures. On the developed film, there are four basic **densities** recognized:

- Gas appears black.
- Fat appears dark grey.
- Water appears light grey.
- Bone appears white.

Hence, an x-ray film really displays a pattern of shadows created by structures in the body lying within the path of the x-rays. Figures 1a and 1b depict normal postero-anterior (PA) and lateral chest x-rays (see below for a discussion of these terms). The borders of a structure will be visualized on an x-ray film only if the radiographic density of the structure is different than that of tissues immediately adjacent to it. Therefore, certain structures are expected to be visible (Figures 1c and 1d contain PA and lateral chest x-rays with the chambers of the heart labelled). For example, the left and right heart borders should be seen on a chest radiograph because the heart, which is water density, is bordered by the lungs, which are gas density. If the heart border is not visible, this suggests that there is a water-density disease process occurring in the lung tissues immediately adjacent to the heart. On the other hand, if there is an abnormal density overlying the heart border but the heart border can still be seen distinctly through the density, the disease process is not immediately adjacent to the heart itself. This loss of visualization of an expected structure is known as the **silhouette sign**. It is important for two reasons. First, it implies the presence of a disease process. Second, it can provide three-dimensional information about a two-dimensional image. For example, both the right middle lobe and right lower lobe project to the right of the right heart border. However, the middle lobe actually touches the part of the heart that forms this border, while the lower lobe is situated more posteriorly. Therefore, if one sees an abnormal opacity beside the heart in the right lung base and the heart border is not visible, then the opacity is in the middle lobe. If the heart border is

Figure 1a. *A normal postero-anterior (PA) chest radiograph.*

Figure 1b. *A normal lateral chest radiograph.*

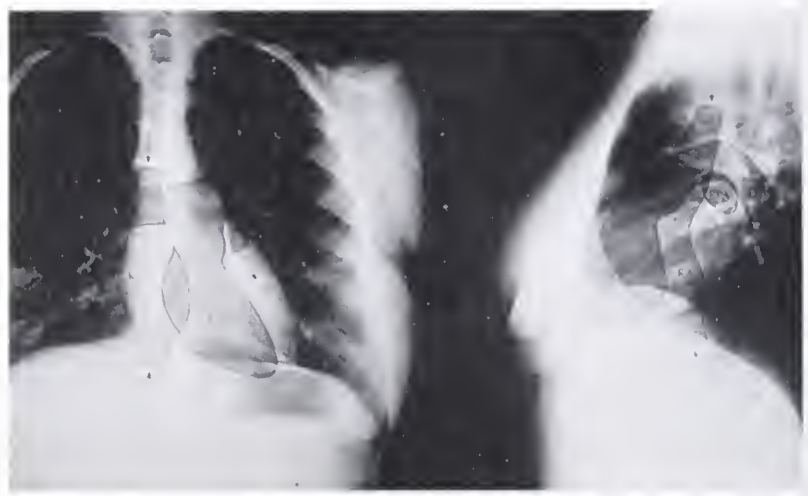

Figure 1c. *Normal PA and lateral chest radiographs. The right atrium and right ventricle of the heart are labelled.*

Figure 1d. *Normal PA and lateral chest radiographs. The left atrium and left ventricle of the heart are labelled.*

still visible, the abnormality is likely in the lower lobe. Figure 2 demonstrates the silhouette sign in a patient with pneumonia and the disappearance of this sign upon successful treatment of the disease.

Postero-anterior (PA) and lateral chest radiographs are the basic standard projections. Other accessory views include an apical lordotic projection, which is useful for small pulmonary lesions in the lung apex that may be obscured by the bony thorax on the PA view. Oblique views are useful for pleural or chest wall lesions. Moreover, the lateral decubitus position (with the patient lying on the affected side and using a horizontal x-ray beam for the PA projection) is a useful technique for detecting small pleural effusions and confirming the gravitational mobility of larger collections.

The following order is suggested in studying chest films. It ensures that no abnormalities will be overlooked. Any order may be used, but one should use the same pattern consistently in order to examine all the structures on every chest film.

Step 1. Scan the Patient Data and Determine the Film Quality.

In approaching a chest x-ray, the first piece of information to note is the "L" (left) marker that signifies the patient's left side to ensure the correct view of the film. The most apparent feature that may suggest a reversed film is the cardiac configuration. An inappropriate cardiac configuration may indicate dex-

trocardia; however, it is more commonly due to human error. The patient's name is an obvious detail that should be verified before proceeding with the interpretation of the film. The ethnic background of the patient may be deduced from the name, which may hint at a disease process that is more prevalent within that ethnic group. Other written data that may be useful include patient's age or date of birth and possibly the hospital ward or department that ordered the film.

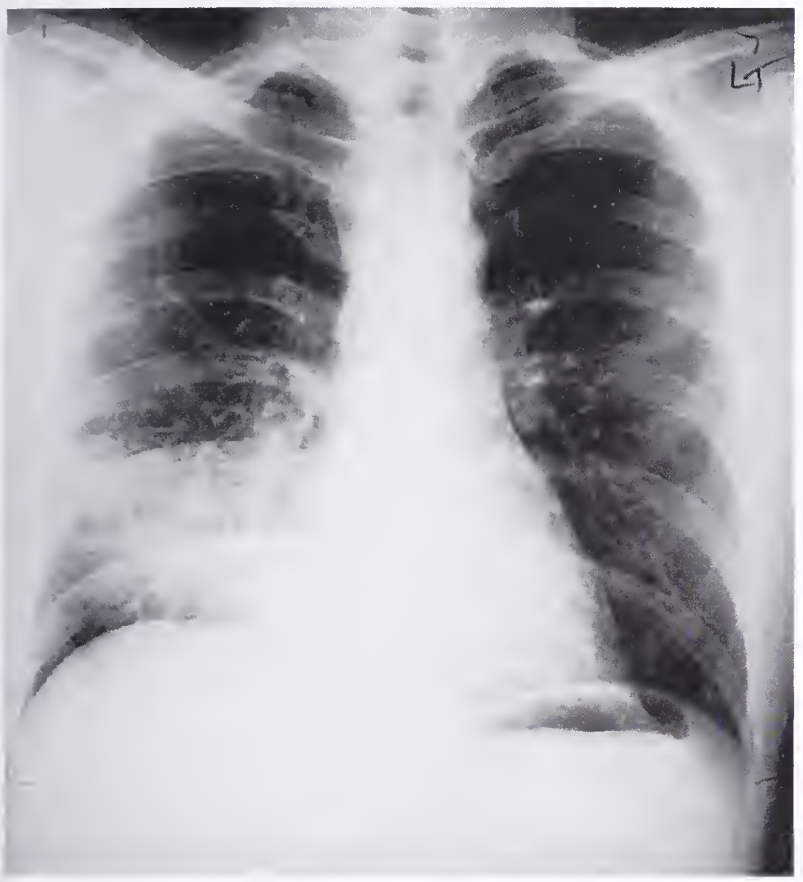

Figure 2a. *PA chest radiograph demonstrating the silhouette sign. In this case, the right heart border is obscured by pneumonia in the right lung. The diseased lung and adjacent heart are of similar density and are therefore indistinct.*

Figure 2b. *Lateral chest radiograph of the same patient as in Figure 2a.*

A number of technical factors should be considered before attempting to interpret any chest radiograph, and they include exposure, inspiration, position, and miscellaneous factors. These features constitute the quality of the film, which is a crucial component in chest radiology.

- **Exposure**. In a correctly exposed film, the degree of penetration should be such that the lower thoracic disc spaces can be clearly seen through the cardiac silhouette. In an underpenetrated film, the intervertebral spaces are not visible through the heart shadow. On the other hand, an overexposed film will be too dark to discern lung vessels.

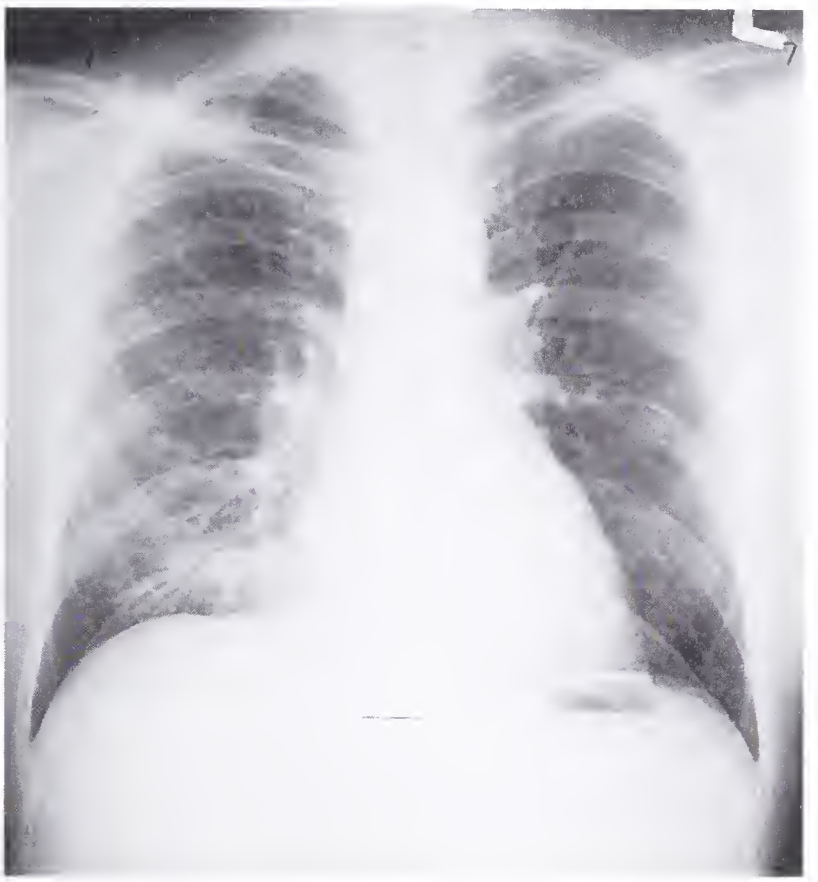

Figure 2c. *PA chest radiograph of the same patient as in Figure 2a after successful treatment of the pneumonia. The right heart border is now distinct.*

- **Inspiration**. Routine chest films are taken while the patient is holding the breath on full inspiration. The dome of the right hemidiaphragm should project over a level between the anterior fifth rib and sixth inter-costal space.

- **Position**. The patient should be positioned such that the coronal plane of the thorax is parallel to the film and at right angles to the X-ray beam. In this position, the spinous processes should project midway between the medial heads of the clavicles. The bony thorax should be the focus when looking for rotation since other midline structures such as the trachea can be shifted in disease. Even slight rotation is undesirable in a chest film because the cardiac and mediastinal shadows will appear distorted.

  The lordotic position is employed to look at the apices of the lungs. The patient leans back such that the medial end of the first rib anteriorly projects above the lung apex as opposed to

the standard radiographic position in which it projects over the medial end of the fourth or fifth rib posteriorly.

- **Miscellaneous factors.** Other possible objects that may be obscuring intrathoracic structures include necklaces, hair braids, and, on lateral view, the patient's arms.

The importance of assessing technical factors before interpreting chest radiographs is illustrated in Figure 3. Figure 3a gives the impression of pulmonary edema, but was actually taken when the patient was not in full inspiration. Figure 3b is a chest x-ray of the same patient in full inspiration, demonstrating an absence of the "edema."

Figure 3a. *Chest radiograph with poor technical quality: the patient was not in full inspiration. This gives the impression that the patient has pulmonary edema.*

Figure 3b. *Chest radiograph of the same patient as in Figure 3a but with full inspiration. Note that the "edema" has vanished.*

Step 2. Examine the Chest Wall.

The radiological assessment of the thoracic cage and its associated soft tissues is an integral part of chest radiology. Radiological changes in the chest wall may be due to a pulmonary disease process. However, they may also represent primary lesions of the bones or soft tissues that may be missed if not looked for specifically.

Vertebral column. When viewing both postero-anterior (PA) and lateral films, the vertebral column should be carefully examined. Each vertebra should be inspected in terms of its body, pedicles, spinous and transverse processes, as well as disc spaces. On lateral projections, the vertebral bodies should get progressively blacker from top to bottom. Spinal deformities such as kyphosis, lordosis, and scoliosis may distort the contours of the chest and can be readily recognized on both views. Other radiological changes in the vertebral column include bony erosions and invasions by intrathoracic tumours.

Ribs. The general shape, direction, symmetry, and spacing of the ribs should be noted. The ribs are roughly parallel with the posterior halves horizontal or slightly downward and the anterior ends curving downwards and inwards. Each rib should be examined individually in its entirety.

A number of different disease processes may involve the ribs. Congenital abnormalities such as cervical ribs or absent ribs are not uncommon. Diseases of the bone can involve the ribs, including tumours or metastases. Rib fractures due to trauma or stress may also be evident. Rib destruction is a radiological sign of bony involvement by an adjacent intrathoracic lesion, most likely a peripheral lung carcinoma.

Clavicles and proximal humeri. Due to their unique curved shape, the shadows of the two clavicles will appear symmetrical on the radiographs only if there is no rotation of the chest. Irregular erosion can sometimes be seen on the inferior aspect of the medial end of the clavicle. This is a normal anatomical appearance called the rhomboid fossa. Abnormalities of the proximal humerus may also be evident on a chest film.

Skin and subcutaneous tissues. Lesions of the skin and subcutaneous tissues that may be recognized include neurofibromata, warts, and subcutaneous emphysema.

Breasts. The presence or absence of breasts should be noted. The shadows cast by female breasts are variable in size and shape. They may be asymmetrical. Nipples may cast rounded shadows that may mimic a pulmonary nodule. Mastectomy usually produces characteristic radiological changes that are often missed.

Soft tissues. The amount of soft tissue present should be inspected to determine if patient is cachectic. Muscles occasionally cast shadows on PA films and these include the sternomastoid and the pectoralis major. Soft tissue shadows

known as companion shadows run closely to parts of the bony thorax and are sometimes present as well. In addition, soft tissue masses may also be evident and should be noted.

Step 3. Examine the Abdomen.

In the abdomen, organ masses and great vessels may or may not be visible depending on the presence of fat surrounding them. The amount of abdomen visible on a chest film is variable. The size of the liver and spleen may be assessed in some cases. Other radiological findings that may be observed include distension of the gastro-intestinal tract, free air under the diaphragm possibly indicating visceral rupture, collections of multiple small gas lucencies suggestive of an abscess, abnormal calcifications, or surgical clips.

Step 4. Examine the Diaphragm.

The diaphragm is a powerful muscle of respiration that consists of a thin muscular sheet. It is attached to the xiphoid, lower six costal cartilages, ribs, and upper lumbar vertebrae. Although the diaphragm functions as a single muscle, it is customary to consider a right and a left leaf. On a PA film, each hemidiaphragm is usually smooth and is horizontal medially with gradual inferior sloping laterally. The point of maximal curvature is normally in the middle third of each hemidiaphragm. Only the upper surface of the diaphragm is visualized on the PA film since the underside of the diaphragm blends into the radiopacity of the upper abdominal viscera. The diaphragm may become visible if there is free air in the peritoneal space separating the diaphragm from other abdominal structures. The point where the diaphragm meets the chest wall laterally on a PA film and posteriorly on a lateral film constitutes a sharp acute angle referred to as the lateral and posterior costophrenic angles, respectively.

The smooth convexity of the diaphragm may appear "bumpy" or "scalloped" in some normal individuals (Figure 4); however, a prominent bulge forming acute angles with the hemidiaphragm usually suggests disease and warrants further investigation. The height of the diaphragm varies considerably with respiration. On full inspiration, the diaphragm is usually seen at the level of the tenth posterior intercostal space or the sixth rib anteriorly. The right hemidiaphragm is normally approximately 2 cm higher than the left hemidiaphragm. Deviation from this position may be due to normal variation but other clues suggestive of pathology should be sought.

Elevation of the diaphragm may be due to a number of conditions including lobar atelectasis, phrenic paralysis, subphrenic infection, and lung diseases associated with volume loss, including pulmonary infarction. Table 1 lists some of the causes of elevation of the diaphragm as seen at radiography and they are divided into bilateral versus unilateral elevation.

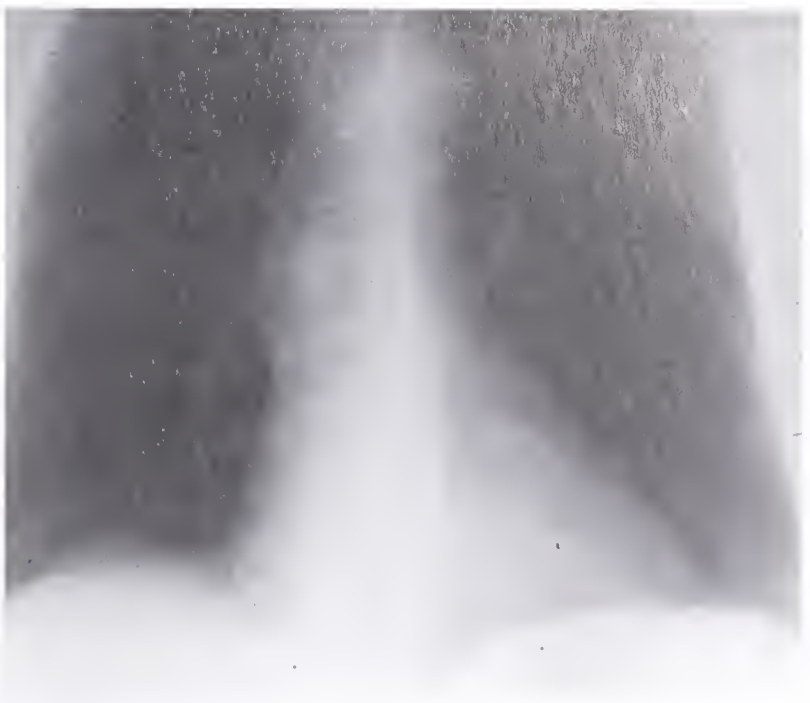

Figure 4. *Scalloping of the right hemidiaphragm.*

Table 1
Causes of Diaphragmatic Elevation

Bilateral Elevation	Unilateral Elevation
Infancy	Scoliosis
Expiration or incomplete inspiration	Phrenic nerve palsy
Supine radiograph	Lower lobe collapse
Obesity	Eventration
Pregnancy	Basal pleural or pulmonary infection
Ascites	Basal pulmonary infarction
Large abdominal mass	Subphrenic infection
Intestinal distension	Subdiaphragmatic tumour
Bilateral intrathoracic or subphrenic infection	

Step 5. Examine the Pleura.

The pleura are thin layers of tissue that envelop each of the pulmonary lobes, forming the fissures where two lobes lie adjacent to one another and line the inner surface of the thoracic cage. Under normal circumstances, aside from the fissures, the pleura is too thin to be seen radiographically; however, it may be visible when it is thickened by disease processes such as inflammation. The pleural space normally contains a small amount of fluid that is not visible radiographically. However, gas and abnormal amounts of fluid in the pleural space can be visualized.

When examining the pleura, the costophrenic angles should be sharp (Figure 5a). Blunting of these angles (Figure 5b) usually indicates pleural effusion or thickening. The entire perimeter of

both lungs should be scrutinized to look for focal or diffuse areas of pleural thickening. Next, the position of the pleural fissures should be determined. The left and right major fissures are usually seen on lateral view only and they run from about T4 in an antero-inferior direction to the junction of the anterior 1/4 and posterior 3/4 of the diaphragm. The right minor fissure is straight or gently curved at about the fifth rib laterally on the PA film and about midsternum on lateral view.

Figure 5a. *Close-up view of a lateral chest radiograph showing a sharp costophrenic angle.*

Figure 5b. *Close-up view of a lateral chest radiograph showing a blunted posterior costophrenic angle.*

Fluid that accumulates with the pleural space may be a clear transudate, a sero-fibrinous or purulent exudate, a hemorrhagic effusion, or a chylous exudate. Radiologically, they cannot be differentiated. Pleural fluid occupies the pleural cavity at the expense of the underlying lung tissues but will also displace the chest wall outward and the diaphragm inferiorly. Pleural fluid first collects under the lung as subpulmonic effusion and it is often seen on the PA film as a shift of the most convex part of the hemidiaphragm from the middle third to the junction of the middle and lateral thirds. As the amount of fluid increases, blunting of the posterior costophrenic angles can be detected followed by the lateral costophrenic angles. Subsequently, increasing fluid density is seen moving up the thorax, obscuring the diaphragm, with the height of the fluid being greatest at the periphery.

Pneumothorax, defined as gas in the pleural cavity, is commonly spontaneous in etiology and it is usually caused by the rupture of a sub-pleural emphysematous bleb or bulla (Figure 6). Air may also escape into the pleural space from the lung following the rupture of a lung cavity or abscess. Another route of entry of air is from the external environment following an artificial pneumothorax or penetrating wounds. Air may also reach the pleural space via the mediastinum or following the rupture of a subdiaphragmatic abscess. Radiologically, a pneumothorax is manifested as the presence of a thin white line representing the visceral pleura that has separated from the chest wall. This is usually seen in the upper hemithorax on an upright film. The underlying lung relaxes and retracts towards the hilum, leaving a clear radiolucent pleural cavity devoid of lung markings. Furthermore, a large pneumothorax may cause mediastinal shift to the normal side.

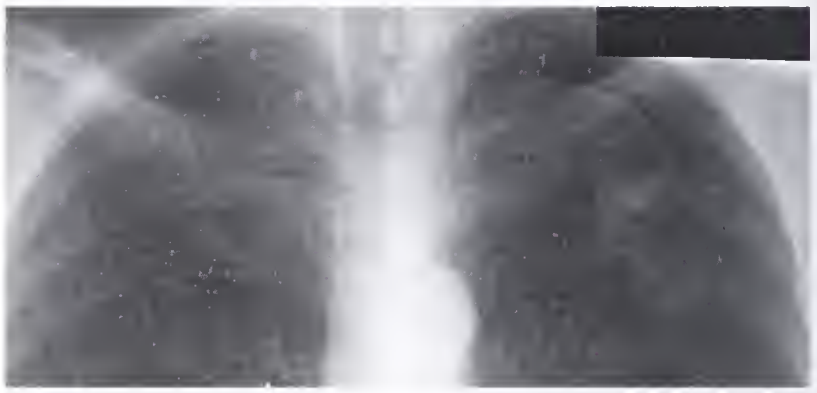

Figure 6. *PA chest radiograph showing a left pneumothorax. The superior margin of the left lung is pulled away from the chest wall.*

Calcification of the pleura can be seen following empyema, hemothorax, or asbestos exposure. Radiologically, irregular sheets of pleural calcification composed of amorphous plaques are observed. The pleural calcification following empyema and hemothorax is usually unilateral and there may be other signs suggestive of the cause, including pulmonary scarring and calcification (i.e., TB) or healed rib fractures. Other signs commonly associated with extensively calcified pleura include pleural thickening, marked tenting of the diaphragm, or filling of the costophrenic angles. In asbestosis, the pleural calcification is usually bilateral and consists of shallow plaques on the diaphragmatic or lower costal pleura.

Step 6. Examine the Heart.

The major presentations of cardiac disease on the chest film are chamber enlargement and abnormal pulmonary vasculature.

Accordingly, when examining the silhouette of the heart, the first step is usually to determine if any enlargement is present. On the PA film, the **cardiothoracic ratio** provides a quantitative estimate of suspected cardiac enlargement. The cardiac diameter is determined by measuring the distance from the rightmost edge of the heart to the midline, and adding that to the distance from the midline to the leftmost edge of the heart; these two line segments are usually not on the same plane. The thoracic diameter is the largest transverse diameter between the inner margins of the ribs. The cardiothoracic ratio equals the cardiac diameter divided by the thoracic diameter. A cardiothoracic ratio greater than 0.5 is a rough determinant of cardiac abnormality in adults, although it can reach 0.6 in children and in elderly patients.

Note that a widened cardiac silhouette cannot be equated with cardiomegaly. The cardiac silhouette can be widened by pericardial disease, or rarely by mediastinal disease, in addition to cardiomegaly. As well, true cardiomegaly can be present with a normal cardiothoracic ratio; for example, if the patient has emphysema and an abnormally large thoracic diameter, then the heart may be enlarged but not to a degree to reach a ratio of 50%.

Different chambers of the heart contribute to different portions of the cardiac silhouette, and consequently enlargement or dilatation of individual cardiac chambers produces characteristic changes on the PA and/or lateral chest films. Figure 7 illustrates generalized cardiomegaly with no specific chamber enlargement, and also reveals enlarged pulmonary arteries. Figures 7b through 7f demonstrate specific chamber enlargement. In general, simple chamber hypertrophy without dilatation can be difficult to detect on plain chest radiographs, since the cardiac silhouette may be of normal size.

Another point worth noting is that many common cardiac diseases do not produce visible changes on plain chest films. Examples include acute myocardial infarction, mild or early valvular disease, as well as restrictive and hypertrophic cardiomyopathy.

Left ventricular dilatation may be due to long-standing systemic hypertension with heart failure, aortic valvular disease, or dilated cardiomyopathy, three of the commonest causes of cardiac enlargement on the chest x-ray. The most striking feature is leftward expansion of the cardiac silhouette with a prominent cardiac apex. On the lateral film, the cardiac silhouette projects posteriorly more than 1.7 cm behind the inferior vena cava, 2 cm above the point of intersection of the latter with the diaphragm. This is known as the **Hoffman-Riggler sign**, and is very specific to left ventricular enlargement. However, it is often difficult to locate the point of intersection of the inferior vena cava with the diaphragm and it is important that the patient is not rotated. As well, if there is enlargement of the right ventricle then it can push the LV posteriorly, so before using this sign, check that the RV is not radiographically enlarged.

Left atrial enlargement may result from mitral valvular disease or ventricular septal defects. Left atrial enlargement can create what appears to be a double right heart border on the PA film, although this may rarely be seen in normal individuals. However, if the distance from the midpoint of the double density to the midpoint of the left main bronchus is greater than 7 cm, left atrial enlargement is likely. Another sign is widening of the angle of the carina, although this sign is also non-specific and is a late finding. Enlargement of the left atrial appendage straightens the left heart border and may even cause a bulge, and must not be confused with enlargement of the pulmonary outflow tract, which is immediately superior to it.

On the PA film, the appearance of right ventricular enlargement may be similar to that of left ventricular enlargement in that both cause enlargement of the cardiothoracic ratio. A distinguishing feature; however, is elevation of the cardiac apex above the left hemidiaphragm, although this is not a common finding in adults. Because early changes of right heart enlargement are difficult to detect on the PA film, the lateral film is especially important. With few exceptions, the mediastinum immediately behind the sternum is normally clear and has the density of air-filled lung. With right heart enlargement, the anterior border of the cardiac silhouette is in contact with the sternum for more than one-third of its height.

Right atrial enlargement is difficult to determine on the chest radiograph until it is very large. When evident, it appears as visibility of the right heart border over a length of at least half that of the mediastinum.

Pericardial diseases can also enlarge the cardiac silhouette. Pericardial effusions can be confused with cardiomegaly because they have a similar density to the heart on the plain film. Hence, the history and other investigations are important. The most likely indication of a pericardial effusion is rapid enlargement or a rapid decrease in the size of the cardiac silhouette. As well, the cardiac contour takes on a globular shape. Other imaging methods such as echocardiography, CT, or MRI are indicated when pericardial disease is suspected.

Direct visualization of the cardiac valves is not possible on plain chest films. However, when mechanical prosthetic valves are present, they are readily demonstrated and serve as useful landmarks. Aortic valvular calcification, which may be present in aortic stenosis, can be seen most readily on the lateral film as a radiodense halo within the cardiac silhouette. Mitral calcification, which may be present with mitral stenosis, may be visible near the left cardiac border. These calcifications must not be confused with the much more common calcification of the mitral and aortic annuli.

Figure 7a. *PA chest radiograph showing cardiomegaly and enlarged pulmonary arteries. Note that the entire heart is enlarged, with no specific chamber involvement. Compare hilar vascular enlargement with hilar enlargement due to lymphadenopathy (Figure 9).*

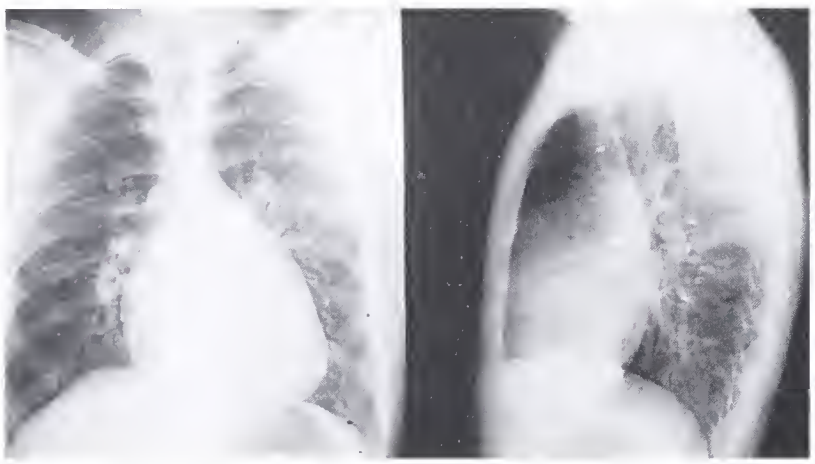

Figure 7b. *PA and lateral chest radiographs illustrating right ventricular enlargement.*

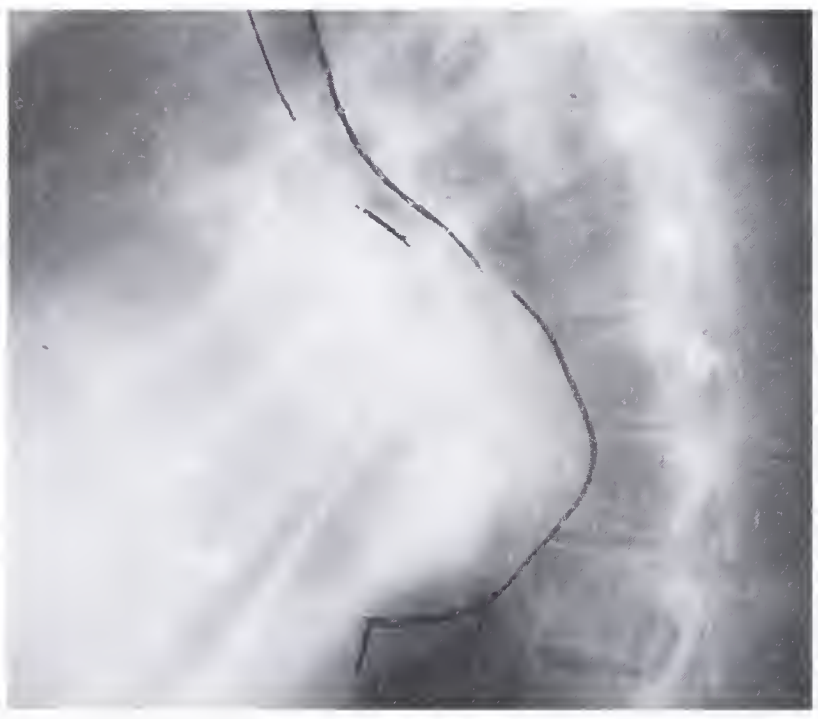

Figure 7c. *Lateral chest radiograph showing left atrial enlargement. Note the line indicating expansion of the heart border a considerable distance posteriorly.*

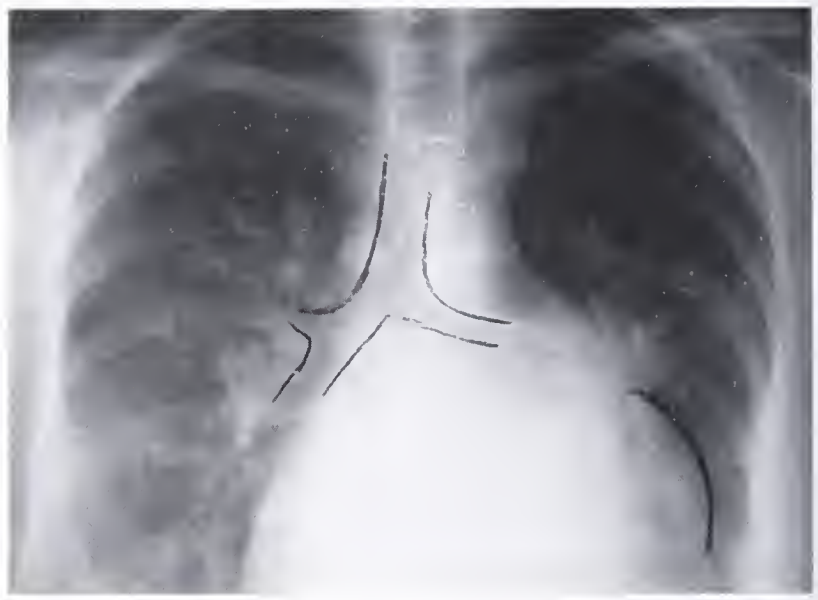

Figure 7d. *PA chest radiograph showing left atrial enlargement. Note the distorted position of the airway as indicated by the lines.*

Figure 7e. *PA chest radiograph demonstrating left ventricular enlargement.*

Figure 7f. *Lateral chest radiograph demonstrating left ventricular enlargement.*

Step 7. Examine the Mediastinum.

The mediastinum is the portion of the thoracic cavity between the lungs. Anatomically, it contains the heart; for the purposes of studying the chest x-ray; however, the heart is considered separately.

Radiologically, it is helpful to divide the mediastinum into the anterior mediastinum (heart and structures anterior to the trachea), posterior mediastinum (spine and paravertebral structures), and middle mediastinum (containing all other mediastinal structures, including the tracheobronchial tree, esophagus, and some pulmonary vessels). This classification is useful because it can be used to narrow the differential diagnosis of a mediastinal mass. Remember that it is difficult to determine which mediastinal compartment contains a lesion without examining both the PA and lateral films, but the silhouette sign can be helpful. Figures 8a (PA film) and 8b (lateral film) reveal an anterior mediastinal mass.

Mediastinal diseases result in changes in the shape and size of the mediastinum focally or as a whole. In particular, mediastinal widening on the PA film is generally indicative of a disease process in the mediastinum. However, a pulmonary mass in contact with the mediastinum can occasionally be difficult to distinguish from a true mediastinal mass. There are many causes of mediastinal masses and as mentioned above, these are best considered in terms of the compartment in which they are present. A list of the more common causes is presented in Table 2.

Figure 8b. *Lateral chest radiograph of the same patient as in Figure 8a, showing the presence of a mass in the anterior mediastinum. This patient was subsequently diagnosed with Hodgkin's disease.*

Figure 8a. *PA chest radiograph demonstrating mediastinal widening.*

Vascular structures are also present in the mediastinum and may be sites of disease. A key landmark on the PA film is the **aortic knob** (or **aortic knuckle**), which appears as a small bulge on the left side of the mediastinum. The aortic knob is the arch of the aorta, and may be seen to contain a ring-shaped density in older individuals, representing calcification. The **aorticopulmonary window** is the portion of the mediastinum that lies between the aortic knob and the left pulmonary artery. Masses in this area are abnormal and usually represent masses in the mediastinum, most frequently lymphadenopathy.

Pneumomediastinum is a condition in which air is trapped in the mediastinum. This gas produces linear, radiolucent streaks within the otherwise radiodense mediastinum. Pneumomediastinum has many causes, including alveolar rupture and dissection of gas along bronchovascular bundles into the mediastinum. It usually occurs during mechanical ventilation, but may also occur in other instances of increased intrathoracic pressure such as coughing, sneezing, and Valsalva manoeuvres. Pneumomediastinum is usually benign and may be associated with pneumopericardium, pneumothorax, and subcutaneous emphysema.

Table 2
Mediastinal Masses

Anterior Mediastinum	Middle Mediastinum	Posterior Mediastinum
Thyroid goitre/carcinoma	Lymphoma	Neural tumours
Lymphoma	Tuberculosis, histoplasmosis	Metastatic lymphadenopathy
Germ cell tumours	Sarcoidosis	Lymphoma
Thymoma	Hiatal hernia	Aortic aneurysm
Pericardial fat	Esophageal diseases	
Aortic aneurysm	Metastatic lymphadenopathy	
	Aortic aneurysm	

Step 8. Examine the Hila.

The hilar regions of each lung can be difficult to assess and therefore must be carefully examined so that lesions are not missed. There are some constant features of the hila that can be used as a framework within which lesions can be identified:

- Typically, the left hilum is 1-2 cm higher than the right; deviation usually suggests lobar collapse or lobectomy.

- The mainstem bronchi are often visible in the superior and medial portions of the hila as tubular structures of lower density than the surrounding hilar tissue.

- The superior portion of the right hilum is formed by a branch of the right superior pulmonary vein and the inferior portion is formed by the right interlobar artery, a branch of the right pulmonary artery.

- The left pulmonary artery arches over the left mainstem bronchus before bifurcating.

- Each hilum looks like a flattened **V**, with the apex pointing medially and located at or lateral to the cardiac silhouette. This structure is called the **hilar angle**. Changes in the contours of the hilar angle are suggestive of disease.

The hila contain vascular structures, lymph nodes, and branches of the airway. The usual causes of hilar abnormalities are pulmonary vascular disease, hilar lymphadenopathy, and focal masses.

In evaluating the hila, consider the density, size, and contours of each. Marked hilar asymmetry or unilateral abnormalities usually indicate the presence of lymphadenopathy or a mass. Bilateral hilar enlargement may be due to bilateral lymphadenopathy or vascular enlargement. When lobulated, this enlargement is likely due to lymphadenopathy while it is likely to be a vascular enlargement when it is smooth.

Hilar lymphadenopathy (Figure 9) has a number of infectious, inflammatory, and neoplastic causes (see Table 3). The appearance of the nodes may give additional clues to the diagnosis. For example, dense calcification suggests a granulomatous process, while eggshell calcification, in which the nodes appear to have only a thin attenuated rim of calcium, is found in only a few diseases, such as silicosis, sarcoidosis, and histoplasmosis.

Figure 9. *PA chest radiograph showing bilateral hilar lymphadenopathy. Compare this radiograph with Figure 7a (bilateral hilar enlargement due to enlarged pulmonary arteries).*

Table 3
Causes of Hilar Lymphadenopathy

Metastatic cancer
(most commonly bronchogenic carcinoma)
Hodgkin's disease
Non-Hodgkin lymphoma
Tuberculosis
Histoplasmosis
Sarcoidosis

Step 9. Examine the Lungs.

The lungs appear dark on the chest film because most of the volume of the inflated lung is gas. The darkness of the lung fields is interrupted by the shadows of the ribs and pulmonary vasculature. The latter appear to branch repeatedly and progressively taper as they course peripherally from the hila. Since the airways are also air-filled, they do not cast shadows on the chest film except for some of the larger ones when seen end-on, in which case their walls attenuate the X-ray beams sufficiently. This is most likely to occur near the hilum.

Air Space Disease

Air space disease refers to any pathological process that results in the replacement of air in the distal air spaces (alveolar sacs and alveoli) with a water density material. These disease processes produce small (5-10 mm), fluffy, and ill-defined nodular opacities called **acinar shadows**. Multiple acinar shadows tend to coalesce, forming larger radiopaque regions.

Another key radiological sign of air space disease is the presence of **air bronchograms**, which occur when alveoli filled with a water-density substance outline air-filled bronchi. Note that air bronchograms may be absent if the disease process has involved the bronchi as well (i.e., mucus, tumour occlusion, etc.). In addition, when some of the alveoli are not involved by the disease process, **air alveolograms** may be seen, and appear as tiny radiolucencies amongst opacified lung tissue. Figure 10 illustrates air space disease.

A variety of substances may fill the alveoli and create air bronchograms and air alveolograms. The determination of the nature of this substance will depend on other radiographic features including location, extent, rapidity of onset and progression, and presence of other abnormalities such as cavitations, as well as the clinical history, physical examination, and further investigations. The most common causes of air space disease are presented in Table 4.

Table 4
Some Air Space Diseases

Substance	Example Diseases
Water or Transudate	Congestive heart failure Drowning Renal failure
Pus	Infection by pyogenic organisms (also *Mycobacterium* spp. and fungal organisms)
Neoplastic cells	Bronchioloalveolar carcinoma Lymphoma
Blood	Thrombocytopenia Blunt chest trauma

Figure 10. *PA chest radiograph demonstrating air space disease. The patient had a right upper lobe pneumonia; note the fissure, forming a crisp interface between the healthy air-filled right middle lobe and the diseased right upper lobe.*

It is also useful to note whether the involvement of air spaces is focal or diffuse. Focal air space disease is commonly due to infection (pneumonia) or neoplastic diseases, while diffuse air space disease is more likely to represent congestive heart failure or adult respiratory distress syndrome. Another clue in the diagnosis of pneumonia is that the spread of the disease is confined by the lung fissures, which may be highlighted as sharp interfaces between radiolucent and radiopaque lung tissue.

Interstitial Disease

Interstitial lung disease is any pathologic process involving the alveolar walls rather than the alveolar air spaces. That is, the alveoli are not filled by the disease process or only minimally affected compared to the interstitium. Except in very severe cases, air bronchograms and air alveolograms are not found. Figure 11a demonstrates an interstitial disease process.

Figure 11a. *Close-up view of a PA chest radiograph demonstrating interstitial disease. Note the reticular or appearance of the lung. This patient had idiopathic pulmonary fibrosis.*

Figure 11b. *Close-up view of a PA chest radiograph demonstrating Kerley B lines, the horizontal striations seen at the margin of the lung. This patient had interstitial pulmonary edema*

When present, an important radiographic finding in interstitial lung disease is the presence of **Kerley B lines** (Figure 11b). These are short, radiopaque, and roughly horizontal lines found in the extreme lung periphery, adjacent to the pleura. They represent interlobular septal thickening in the lung. Kerley B lines are distinguished from the pulmonary vasculature because the latter does not extend to the pleura and because Kerley B lines do not taper and branch. The most common cause of Kerley B lines is congestive heart failure with interstitial edema, but the finding of Kerley B lines is not specific to this disorder since they may occur in other interstitial lung diseases.

Interstitial lung disease is classified on the basis of the radiographic pattern seen (see Table 5).

- The **reticular** pattern consists of very thin (1-2 mm), well-defined linear densities, often arranged in a meshwork pattern. Kerley B lines are included.
- The **nodular** pattern consists of small nodular densities 2-3 mm in diameter scattered within the lung parenchyma. In distinction to acinar shadows, which are also nodular, these are smaller, more well defined and do not coalesce.
- The **mixed** or **reticulonodular** pattern is a combination of reticular and nodular patterns. It must be stated that any reticular disease may at times appear reticulonodular since a line seen end-on can appear as a tiny nodule.

Table 5
Some Interstitial Lung Diseases

Pattern	Example Diseases
Reticular	Congestive heart failure (also with Kerley B lines)
	Idiopathic pulmonary fibrosis
	Radiation fibrosis
	Drug-induced fibrosis
Nodular	Miliary tuberculosis
	Pneumoconioses (silicosis, coal worker's pneumoconiosis)
	Histoplasmosis
	Coccidioidomycosis
	Sarcoidosis
Reticulonodular	Sarcoidosis
	Hypersensitivity pneumonitis
	Asbestosis (almost always associated with other lesions)
	Mycoplasmal pneumonia

Some lung diseases have both an intra-alveolar component and an interstitial component. In these instances, air bronchograms and acinar shadows are present in addition to interstitial patterns. Examples of these diseases include pulmonary edema, bronchioloalveolar carcinoma, sarcoidosis, lymphoma, and bronchiolitis obliterans with organizing pneumonia.

Atelectasis

Atelectasis is the collapse, in whole or in part, of a lung. It is

similar to air space disease in the sense that both processes produce airless alveoli. The difference between the two is that in atelectasis, the air is lost (expelled or absorbed) and not replaced by another substance. This results in a loss of lung volume.

Figure 12a. *Atelectasis. This PA chest radiograph reveals collapse of the right upper lobe. Note the increase in density and the shift of the adjacent lung fissure upward.*

Figure 12b. *Lateral chest radiograph of the patient in Figure 12a.*

The direct radiologic sign of atelectasis of a lobe is the displacement of lung fissures bordering that lobe (Figures 12a and 12b). When fissural displacement is not obvious, additional signs of atelectasis may be helpful but are not necessarily diagnostic. These indirect signs include:

- Increased radiopacity in the atelectatic lung tissue;
- Hilar displacement (normally the left hilum is 1-2 cm higher than the right);
- Mediastinal shift (usually the trachea with upper lobe collapse and the heart with lower lobe collapse);
- Compensatory hyperinflation (other parts of the lungs expand to take the place of the collapsed lobe, especially the lung closest to it; this is manifested as increased radiolucency and is most evident in the adjacent lobe(s) compared to the contralateral lung);
- Elevation of the ipsilateral hemidiaphragm.

The causes of atelectasis are described as obstructive, adhesive, cicatrizing, and passive. These are summarized in Table 6.

Table 6
Types and Causes of Atelectasis

Type	Mechanism	Examples
Obstructive	Lesion blocks air flow to a small lung region, a lobe, or an entire lung	Asthmatic mucous plugs Foreign bodies Endobronchial tumours
Adhesive	Lack of resistance to collapsing forces in alveolar walls causes alveolar closure	Radiation pneumonitis Surfactant deficiency
Cicatrizing	Scarring following an inflammatory process causes contraction of lung tissue	Tuberculosis Pneumoconioses
Passive	An intrathoracic space occupying lesion causes a local reduction in negative intrathoracic pressure allowing lung elastic fibres to shorten thereby reducing the size of air spaces	Emphysematous bullae Pneumothorax Hydrothorax

Pulmonary Nodules or Masses

When confronted with a solitary pulmonary nodule, the main consideration is whether the lesion is benign (as in Figure 13a) or malignant (as in Figure 13b). The radiological signs of malignant and benign nodules are summarized in Table 7. A nodule is generally considered benign if it exhibits a benign calcific pattern or it exhibits no growth over a 2-year period.

Table 7
Signs of Malignant and Benign Nodules

Physical Characteristics	Malignant	Benign
Margins	Not well-defined, spiculated ("corona radiata")	Usually well-defined (but so are metastases)
Contour	Lobulated	Spherical (but so are metastases)
Calcium	None	Central nidus, lamellated, "popcorn", diffuse
Growth Rate	Doubling time of 10 – 465 days	Doubling time < 10 or > 465 days
Associated Signs	Lymphadenopathy, bone destruction, pleural effusion	

The three most important causes of a solitary pulmonary nodule are granulomas, malignant tumours, and hamartomas, in order of frequency. Lesions also included in the differential diagnosis of solitary pulmonary nodule are metastatic tumours, carcinoid and other neuroendocrine tumours, arteriovenous malformations, round atelectasis and other miscellaneous lesions.

Figure 13a. *Close-up view of a chest radiograph showing a small, well-circumscribed pulmonary nodule. This mass was benign.*

Figure 13b. *Close-up view of a chest radiograph showing an ill-defined pulmonary nodule. This nodule was later determined to be malignant.*

Pulmonary versus Extrapulmonary Disease

Pulmonary disease refers to diseases of the lung parenchyma and airways, whereas extrapulmonary disease (for this discussion) involves structures outside the lung that cause mass effects on it. The distinction between extrapulmonary and pulmonary diseases becomes difficult in the case of a peripheral lesion. Some useful signs in determining if a peripheral lesion is inside the lung (pulmonary) or outside but bulging into the lung (extrapulmonary) are presented in Table 8. Figure 14 is an example of an extrapulmonary lesion that might initially be confused with pulmonary disease.

Figure 14. *Close-up view of a PA chest radiograph showing an extrapulmonary mass impinging on the lung. The patient had an intercostal lipoma.*

Table 8
Pulmonary versus Extrapulmonary Disease

Signs	Pulmonary	Extrapulmonary
Angle between lesion and chest wall	Acute	Obtuse
Homogeneity of density	May have air bronchograms	Uniform density (not specific)
Border with air-containing lung	Well or ill-defined	Very well defined margin convex toward lung

Conclusion

The chest x-ray is an invaluable source of information and an indispensable diagnostic tool in medicine. The careful examination of the chest radiograph constitutes an essential component in the management of a number of different diseases. In order not to miss important yet subtle findings, a consistent and organized method should be followed at every encounter. The systematic approach to the chest film presented here can serve as a guide for the novice reader to further develop and adopt his or her own style.

Acknowledgement

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References

1. Felson B, Weinstein AS, and Spitz HB. (1965). *Principles of Chest Roentgenology.* W.B. Saunders Company: U.S.A.
2. Meholic A, Ketai L, and Lofgren R. (1996). *Fundamentals of Chest Radiology.* WB Saunders: Philadelphia.
3. Putman CE, Ravin CE, *et al.* (1994). *Textbook of Diagnostic Imaging 2nd ed. Vol 1.* W.B. Saunders Company: U.S.A.
4. Squire LF and Novelline RA. (1988). *Fundamentals of Radiology 4th ed.* Harvard University Press: U.S.A.
5. Sutton D (ed). (1980). *A Textbook of Radiology and Imaging 3rd ed. Vol. 1.* Churchill Livingstone Inc: Great Britain.

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Evidence-Based Medicine

Practicing Evidence-Based Medicine

Evette Weil, B.A. (OT2)

This article, the fifth in the *UTMJ* series on evidence-based medicine (EBM), examines the initial steps in the implementation of EBM into everyday clinical practice. The goals of EBM are to encourage physicians to ask clinical questions, seek answers from the best available evidence in the literature, and integrate this evidence with their clinical expertise and their patients' values.

Introduction

The practicing clinician is confronted with many questions about diagnosis, therapy, prognosis, and the etiology of diseases. One study found that general practitioners encounter two clinically important questions for every three patients seen.[1] Traditionally, attempts to answer these questions would involve the use of a textbook. Conventional textbooks, however, are often out of date even at the time of publication; therefore, physicians must look elsewhere for the most current and accurate information. Unfortunately, the leap from clinical query to substantiated answer can be a time-consuming process. Given the time constraints of physicians and students, EBM must be practiced efficiently. The intent of this article is to present a logical scheme for approaching clinical questions and to suggest ways to increase the value and efficiency of the literature search.

EBM is broadly comprised of three separate stages: finding the evidence, evaluating the evidence, and applying the evidence to the patient. This article will primarily address the first stage: the search. Identifying the evidence can be further divided into three steps: (1) defining the question; (2) choosing the literature resources; and (3) choosing the best evidence. The clinical scenario described below will be used to elucidate the three stages.

Clinical Scenario

It is the middle of winter. As a family physician, much of your day is spent seeing patients with upper respiratory tract infections. One of your patients asks you whether taking zinc would help her recover from her current bout with the common cold. You have heard about this treatment, but you do not know how to authoritatively answer her question.

1. Defining the Question

Just as formulating the question is the most important step in conducting research, defining the clinical question is the most crucial step in practicing EBM. The success and the ease of the search will depend entirely on whether the clinician has asked an answerable question. Four elements of the question must be consciously considered: (1) the patient or problem being addressed; (2) the intervention; (3) a comparison intervention when applicable; and (4) the outcomes of interest. By outlining these before beginning the search, the clinician can more effectively sort through potential articles to find the ones most relevant to the specific patient and question. In our case, we may define the question as follows: "For a generally healthy patient suffering from an uncomplicated upper respiratory tract infection, will zinc supplements reduce the severity of the infection and speed recovery?" Here we have defined the patient, the problem, the intervention, and two outcomes.

The physician should also predetermine the type of evidence that will be most useful, considering specifically the study design and outcome measures that will best answer the clinical question. For example, if we are investigating the therapeutic benefit of zinc, we may only be interest-

ed in studies that compare zinc to placebo. We can, therefore, increase the specificity of our search by limiting our query to randomized controlled trials or reviews of such trials. Similarly, if we are investigating a diagnostic test, we may limit our search to studies reporting sensitivity, specificity, and positive predictive value.

2. Choosing Resources

The number and types of resources available for the practice of evidence-based medicine is expanding rapidly. So rapidly, in fact, that many of the best resources are not known to the majority of clinicians. Most physicians and medical students look to two conventional sources for clinical information: textbooks and MEDLINE. Both of these resources can be highly valuable, especially EBM-oriented textbooks that are frequently updated and that use judiciously applied searches. In addition, many novel resources, often available over the Internet, have recently been created. It is not feasible to comprehensively describe all available resources here. Instead, this article will highlight some of the most useful clinical resources for the day-to-day practice of EBM. For a broader list of resources, see the introductory article in this series.[2]

2.1 PubMed-MEDLINE

PubMed is an Internet interface for MEDLINE. MEDLINE is a bibliographic database of health care articles maintained by the National Library of Medicine in the United States. Physicians can access MEDLINE from multiple Internet portals, including PubMed, Ovid, and Grateful Med. The choice of portal can significantly affect the ease and success of the search. Here we will examine some of the most helpful features of the PubMed system, which is available free over the Internet (http://www.ncbi.nlm.nih.gov).

The PubMed system offers two services that can dramatically increase yield while decreasing search time. The first of these is the *Clinical Query* option, which aids the physician in appropriately limiting the search. Using this option, the search can be focused on diagnosis, therapy, prognosis, and etiology. In addition, the searcher can decide whether he or she wants to place the emphasis on the sensitivity or specificity of the search. By highlighting sensitivity, PubMed will cast a wide net to capture all potentially relevant articles. By choosing specificity, the program will limit the results to those articles which appear to be most pertinent.

Using our clinical scenario as an example, we can run a *Clinical Query* in PubMed with the terms, *zinc* and *common cold*. We can also specify that the search should focus on treatment, and stress specificity over sensitivity. Such a search generates 14 "hits," a number that can be managed easily by a busy physician or medical student.

A second helpful feature for increasing the total number of studies is the list of *Related Articles* generated by PubMed. PubMed uses medical subject headings (MeSH) to group together studies of similar design and subject matter. Therefore, if you find one article that directly answers your clinical question, you can click on *Related Articles* to identify additional examples. This feature is particularly helpful if you do not initially enter the best search terms. If, by chance you find an article that answers your question, you can then locate other articles with the PubMed system.

2.2 SUMSearch

Another easily accessible source of information is Medical SUMSearch run by the Society for General Internal Medicine at the University of Texas Health Sciences Center San Antonio (http://sumsearch.uthscsa.edu/searchform45.htm). This program searches five sources of information: the Merck Manual, traditional reviews or editorials, systematic reviews, guidelines, and original research. Most of these "hits" are linked to full-text articles via PubMed, the National Guideline Clearinghouse, or the Database of Abstracts of Reviews of Effectiveness. Additionally, like PubMed, the search can be focused on treatment, diagnosis, prognosis, or etiology.

By entering *common cold* and *zinc*, with a focus on treatment, SmartSearch gives a range of citations including: five chapters from the Merck Manual, one traditional review, one practice guideline, six systematic reviews, and 45 original research documents. This is a larger array of material than was generated with the PubMed clinical query, but it has the advantage of specifying the source and type of information. The task of choosing between the different information sources will by discussed in the next section.

2.3 ACP Journal Club

The American College of Physicians Journal Club offers a quick and easy route to finding answers (http://www.acponline.org/journals/acpjc). The ACP Journal Club is a publication that reviews the major clinical journals and abstracts information from key articles. Abstracted articles are selected on the basis of the quality of the study and the clinical relevance of its outcomes. Thus, the ACP Journal Club provides clinicians with an efficient means to stay abreast of the literature. The contents of the ACP Journal Club and its sibling journal, Evidence Based Medicine, are available on a CD-ROM called *Best Evidence* and through Ovid EBM Reviews.

The ACP Journal Club has a somewhat limited role in answering specific clinical questions, because it will only provide information if an applicable study has been reviewed. Therefore, it is quite likely that a search will not

ensure any "hits." However, if applicable articles have been reviewed, then the ACP Journal Club can be useful in a number of ways. The abstracted data is short, easy to read, emphasizes the consequential aspects of the study design and results, and is followed by commentary from an expert in the field. Therefore, the reader can be confident that the study is of high quality and is also provided with insight into the significance of the article. These advantages must be weighed against the disadvantages of not providing a comprehensive survey of the available literature.

In the search through *Best Evidence* for the common cold, there was one abstract of a systematic review. The abstract clearly delineated the question, data sources, study selection, data extraction, main results, and conclusion. There was also commentary, which helps the reader understand how to interpret the results of the meta-analysis and, ultimately, whether physicians should recommend zinc therapy.

3. Choosing the Evidence

The final step in the search is to choose the sources of evidence to further evaluate and transfer into clinical practice. The types of evidence vary from highly synthesized data sources to original studies that need more interpretation on the part of the physician. Each class of evidence along this spectrum offers particular advantages and disadvantages to the clinician wishing to practice EBM.

Guidelines are often taken as the gold standard in practice. They represent multiple forms of information and are generally applicable to the average patient. The process of writing guidelines is complicated and lengthy, and the results represent not only a broad summary of the medical literature, but also the consensus opinion of many experts in the field. Because they offer specific directives, physicians often rely on guidelines to determine practice. There are, however, inherent problems with guidelines, which are frequently overlooked by physicians. First, because preparing guidelines is an enormous and time-consuming project, guidelines do not always represent the most current research. Second, in areas where evidence is insufficient, guidelines sometimes offer directives based on small studies or solely on the committee's opinion. The best guidelines clearly identify the quality of evidence underlying the particular recommendation.

Systematic reviews and meta-analyses are an additional source of synthesized evidence. Like guidelines, they offer the advantage of providing easy access to multiple important articles. A good systematic review or meta-analysis will clearly define the criteria used to select studies, the main sources of heterogeneity between articles, and how this heterogeneity was managed if results were combined to generate a summary effect size. These forms of evidence are convenient for the busy physician, and reduce the bias associated with considering a small number of studies. However, it should be noted that because research in the same area may utilize highly disparate study designs, it may be difficult to combine results. Therefore, even in a field with satisfactory studies, a meta-analysis may not be able to generate definitive results.

Finally, the physician may find that the best evidence is found in reports of individual studies. The advantage of this type of evidence is that it obviates the problems associated with inadequately prepared guidelines or systematic reviews. However, the onus is on the physician to evaluate the quality of the research and the significance of the findings. This obviously requires far more effort from the physician than simply reading a more synthesized form of evidence. The time demands of reading multiple articles and appraising the data may be more than what is feasible for the average physician. However, in many cases, this may be the only available form of evidence because guidelines and systematic reviews only cover a small proportion of clinical questions.

Conclusion

There are a multitude of resources available to the physician wishing to incorporate evidence-based medicine into his or her practice. However, it is important to consider that one's approach to these resources determines whether EBM will be a successful and sustainable part of continuing education and patient care. First and foremost, answerable questions need to be asked. Secondly, the best sources of information must be utilized. Newer forms of print publications and Internet databases can dramatically simplify the process of finding evidence and make EBM a feasible aspect of everyday medical decision-making. Finally, the expansion of synthesized forms of data - guidelines, systematic reviews, and meta-analyses can be invaluable in securing a foundation of evidence for clinical practice - when used appropriately.

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References

1. Covell DG, Uman GC and Manning PR. (1985). Information needs in office practice; are they being met. *Ann Intern Med.* 103:596-599.
2. Weil EW. (1999). From clinical trials to the clinic. *UTMJ.* 76:144-146.

Exploring a Pediatric Exanthem

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Introducing Morning Report

Morning Report is a traditional round in most internal medicine training programmes. While the specific format of Morning Report varies between institutions, it typically involves the presentation of a clinical case followed by a case-oriented discussion. At the University of Toronto, the goals of Morning Report are to facilitate teaching and learning at various levels of medical training, to promote social interaction between the medical faculty and the medical housestaff, and to discuss issues related to local hospital structure and function. Traditionally, the medical team that was on-call the night prior to Morning Report presents a clinical case from the previous day's admissions. A staff physician then leads a discussion of the case with the goal of emphasizing the clinical reasoning process involved in the diagnosis and management of the patient's condition. Discussion focuses on the generation of a provisional and differential diagnosis for the presenting complaint, refinement of the provisional diagnosis as additional information becomes available, the anticipation of laboratory and radiological findings, and principles of management of the condition.

The Scene

A conference room in a Toronto teaching hospital. Students, residents and staff physicians are seated around a large table. Jonathan, a third year medical student, and Jessica, a second year resident (PGY-2), have worked overnight admitting patients to the hospital. They have selected one case from the previous night's admissions, which they will now present to the group. A faculty member, Dr. Chang will facilitate a discussion of the case.

Jonathan: This 10-month-old girl presented to the emergency room because of a fever and a rash. The fever started approximately one week ago and was documented by the parents at 40°C, measured rectally. She became irritable, ate poorly, and had a nonproductive cough, and coryza. The maculopapular rash started about 4 days ago in the groin area but soon became generalized. She presented to her family doctor 3 days ago, when she was given erythromycin and acetaminophen. Although the rash has begun to clear (see Figure 1), the temperature still ranges between 38.6°C and 40.8°C.

Figure 1. *Photograph of hand showing a maculopapular rash.*

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Dr. Chang: Fevers and rashes are fairly common occurrences in the pediatric population. What is the differential diagnosis for an infant with a febrile exanthem?

Jonathan: The commonest pediatric exanthem is chicken pox, but one must also consider the nature of the exanthem. With a maculopapular rash, measles, rubella, roseola, scarlet fever, and Kawasaki's syndrome are clear possibilities. Staphylococcal scalded skin syndrome or meningococcemia would be considerations if the rash were bullous or petechial.

Dr. Chang: Excellent, those are some of the classic pediatric exanthems. But clinically, one must also consider other origins of the exanthem such as drug reactions, allergic reactions, and signs of systemic disease such as juvenile rheumatoid arthritis. Let's continue with the history in order to try and narrow down our differential diagnosis.

Jonathan: The girl and her older brother had chickenpox two months ago. One month ago she had an episode of a mild fever and a scarlet fever-like rash. The mild fever and rash resolved within a few days of onset but the skin on her arms and legs began to peel. The girl's immunizations were up to date, she was on no other medications, and there was no history of travel or exposure to sick persons, or animals. There was no family history of allergy. The pregnancy and delivery were uncomplicated.

Jessica: So this exanthem is likely not due to chicken pox. The mild fever and rash one month ago may lead us to think of something more chronic rather than acute or they could be unrelated. The immunizations were up to date, but the MMR vaccine is not given until 1 year of age. The lack of exposure to sick persons or animals makes infectious causes slightly less likely. An allergic or drug reaction to erythromycin is not likely as the rash started before the erythromycin was given. As well, there was no evidence of congenital or chronic disease. We also forgot to point out that the mother mentioned she thought that the baby's lips were swollen and the tongue was redder than usual.

Dr. Chang: That is a very important point because it starts to make us focus on certain diagnoses. Jonathan, do you know what we are thinking about?

Jonathan: Considering the rash I think that the glossitis makes one think about Kawasaki's or…anemia?

Jessica: I think that glossitis associated with macrocytic anemia sounds more unlikely given the clinical picture. With pediatric exanthems and glossitis, the important distinction to make is between Kawasaki's syndrome and scarlet fever.

Dr. Chang: What are the diagnostic criteria for Kawasaki's syndrome?

Jonathan: The diagnostic criteria comprise fever of at least five days' duration and four of the following five findings:

1. Bilateral non-purulent conjunctivitis
2. Oral changes (strawberry tongue, oropharyngeal redness and lip cracking)
3. Cervical lymphadenopathy, usually unilateral
4. Redness of palms/soles, edema of fingers/toes and desquamation of fingers/toes during convalescence
5. Polymorphous erythematous rash, often with perineal accentuation

Dr. Chang: Excellent. Now tell me about the prognosis and treatment of Kawasaki's syndrome.

Jonathan: The main complication of Kawasaki's syndrome is the development of coronary artery aneurysms that occur in almost a quarter of untreated patients. These may lead to sudden death. The treatment involves a single high dose of intravenous immunoglobulin and long-term administration of aspirin.

Dr. Chang: What about scarlet fever?

Jessica: Scarlet fever is caused by group A streptococci. It is characterized by an incubation period of two to four days followed by fever, headache and tonsillitis. A macular rash develops with increased density in the neck, axillae, and groin. Desquamation occurs on the hands and feet and tends to be fine flaking of the skin but may peel in sheets. A thick white coating develops on the tongue that eventually peels and reveals a strawberry tongue.

Dr. Chang: So tell me about the physical exam.

Jessica: Her temperature was 39.7°C, her pulse was 120, respirations were 46 and her blood pressure was 115/65. Examination revealed a diffuse erythematous rash with desquamation on the legs, toes and fingers with cervical, axillary and inguinal lymphadenopathy. The conjunctivae were injected, there was swelling, redness and cracking of her lips, and the tongue and pharynx were reddened. The otoscopic and ophthalmoscopic examinations were normal. The lungs were clear and the heart was normal.

Dr. Chang: So do you think that this infant has Kawasaki's syndrome or scarlet fever?

Jonathan: Her fever, rash, conjunctivitis and oral changes are supportive of the diagnosis of Kawasaki's syndrome. However, the locations of the desquamation are atypical and the lymphadenopathy is diffuse and not confined to the cervical area. The desquamation in this case is more typical of scarlet fever. However, no evidence of tonsillitis was found and a thick white coating on the tongue was never noticed.

Dr. Chang: So in this case we are really not very sure if this is scarlet fever, Kawasaki's syndrome, or something else. So tell me about the lab work, investigations and tests.

Jonathan: The urine was mildly positive for protein and for ketones. The sediment contained no red cells, 3 to 4 white cells and a few bacteria per high-power field. Urine, blood and throat cultures were taken. Laboratory tests were performed (Table 1). Radiographs of the chest revealed pneumonia in the right upper lobe with a small pleural effusion (Figure 2). The oxygen saturation was 99% on room air.

Jessica: The severity of this child's fever, its lack of response to antimicrobial agents, and the pulmonary infiltrate raise the possibility of tuberculosis. A careful history of the family, which had emigrated from Haiti, revealed that the father might have been exposed to tuberculosis many years ago and might have received treatment with isoniazid.

Dr. Chang: So what do we want to do if we suspect tuberculosis?

Table 1
Laboratory Findings

Hematocrit	33%	Differential (%)	
MCV (μm^3)	75		
ESR (mm/hr)	81	Neutrophils	55
Smear Results	hypochromia (+)	Lymphocytes	35
	microcytosis (++)	Monocytes	9
WBC (per mm^3)	20 600	Eosinophils	1
Platelets (per mm^3)	614 000		
AST (U/liter)	24		
Alk phos (U/liter)	119		

Figure 2. *Chest radiograph showing dense consolidation in the right upper lobe and hilum with an adjacent pleural effusion.*

Jonathan: In considering tuberculosis, in addition to the chest radiograph, we would want to perform a tuberculin skin test, obtain sputum samples and perhaps perform a thoracentesis in order to obtain fluid from her pleural effusion.

Dr. Chang: Sputum samples?

Jessica: I think that Jonathan is referring to aspiration of gastric contents while the child is fasting or bronchoalveolar lavage because infants cannot expectorate sputum.

Jonathan: Yes...we also found some very interesting papers in our Medline search which indicate a high rate of false-positive tuberculin tests in both typical cases of Kawasaki's syndrome and streptococcal infection.

Dr. Chang: Okay, so that may confound the results of our skin test. Are there any other symptoms here that may make it difficult to diagnose tuberculosis?

Jessica: The cutaneous findings in this child are difficult to attribute to tuberculosis. The characteristic skin manifestations of tuberculosis are erythema nodosum and tuberculids which are the result of disseminated infection. Our Medline search revealed no previous case reports noting an association between tuberculosis and a diffuse erythematous rash with subsequent desquamation.

Dr. Chang: So tell me what you think is happening here.

Jonathan: We see three main possibilities. Kawasaki's syndrome, group A streptococcal infection, or tuberculosis.

Jessica: If we are considering Kawasaki's, the pneumonia must be considered bacterial in origin – probably pneumococcal or staphylococcal. If we attribute the symptoms to streptococcus, then we must question the lack of response to antibiotic therapy. If this child has pulmonary tuberculosis, we would need a second explanation - either Kawasaki's syndrome or streptococcal infection - in order to explain the rash and mucosal abnormalities.

Dr. Chang: So what do you suggest we do?

Jessica: In terms of investigations, I would suggest an echocardiogram in order to look for evidence of coronary artery aneurysms consistent with Kawasaki's syndrome. We are also waiting for the blood, urine and throat culture results. We must also wait to see the results of the tuberculosis investigations. In the meantime, the duration of this child's fever, the relatively high frequency of atypical Kawasaki's syndrome in infants, the low toxicity of therapy, and the importance of preventing coronary artery aneurysms would warrant the administration of immunoglobulin and aspirin.

Dr. Chang: That sounds like a reasonable idea. Thank you for presenting this case.

Follow-up

Gastric aspiration and fluid from the pleural effusion did not provide any acid-fast bacilli on smear or culture. However, the bronchoalveolar lavage provided material showing beaded acid-fast bacilli, which proved to be *Mycobacterium tuberculosis* on culture. The infant was discharged while receiving isoniazid, rifampin, pyrazinamide and ethambutol and she is now clinically well.

Clinical Pearls

1. It is always important to search thoroughly for systemic symptoms and signs when considering the etiology of a rash.

2. When suspecting Kawasaki's syndrome in infants, the low toxicity of therapy and the importance of preventing coronary artery aneurysms would warrant the early administration of immunoglobulin and aspirin.

3. With increasing prevalence of tuberculosis and a larger number of immigrants from poorer countries, it is important to maintain a high index of suspicion for tuberculosis.

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References

1. Shulman ST, De Inocencio J, and Hirsch R. (1995). Kawasaki disease. *Pediatr Clin North Am.* 42:1205-1222.
2. Rosenfeld EA, Corydon KE, and Shulman S. (1995). Kawasaki disease in infants less than one year of age. *J Pediatr.* 126:524-529.
3. Takayama J, Yanase Y, and Kawasaki T. (1982). A study on erythematous change at the site of the BCG inoculation. *Acta Pediatr Jpn.* 86:567-572.
4. Chartrand SA and McCracken GH. (1982). Staphylococcal pneumonia in infants and children. *Pediatr Infect Dis.* 1:19-23.
5. Hendgren WH III and Haggerty RJ. (1958). Staphylococcic pneumonia in infancy and childhood. *JAMA.* 168:6-16.
6. Miller J and Wallgren A. (1939). *Pulmonary Tuberculosis in Adults and Children.* Thomas Nelson: New York.
7. Smith MHD and Teele DW. (1995). Tuberculosis. *In: Infectious diseases of the fetus and Newborn infant, 4th ed.* Remington JS and Klein JO (eds). WB Saunders: Philadelphia, pp. 1074-1086.
8. Husson RN and Mark EJ. (1999). A 10-month-old girl with fever, upper-lobe pneumonia, and a pleural effusion. *NEJM.* 341:153-160.

'Pseudomyxoma Peritonei: The Case of the Perplexed Primaries'

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Case Presentation

A 49-year-old woman with a recent history of a pelvic mass was referred for an oncology consult.

Six months prior: The patient presented to her family physician with lower abdominal discomfort and bloating. The patient had normal energy, and did not complain of weight loss, nausea, vomiting, fever, night sweats, or change in appetite. However, over the next few months, she experienced inereasing abdominal girth with associated fullness and abdominal pain.

Over the next several months, several ultrasound (U/S) examinations were performed. The first U/S of the abdomen revealed ascites and the radiographic appearance of peritoneal carcinomatosis. Twelve days later, a repeat abdominal U/S and a trans-pelvic U/S revealed the presenee of a large mass on the left ovary. The mass appeared cystic in nature, with associated peritoneal carcinomatosis and two solid tumour implants on the serosal surfaee of the liver. There were no discernible intrahepatic metastases and the remainder of the study was unremarkable.

The patient had a past medical history of mild cervical dysplasia that had resolved without treatment. She has had two uncomplieated vaginal deliveries, has been post-menopausal for one year, and was not receiving hormone replacement therapy. She had no prior history of breast or ovarian eaneer. The patient is a non-smoker, married with two children, and had worked as a fitness instructor until the time of her illness. Her maternal family history is positive for eaneer; her aunt was diagnosed in her fifties with ovarian caneer, and her grandmother had eolon cancer.

What is the differential diagnosis to explain the clinical findings of ascites and a pelvic mass?

Differential Diagnosis

Ascites. Ascites is defined as the accumulation of excess fluid within the peritoneal cavity. Historically, ascites was typically classified as either transudative or exudative, however, the serum-aseites albumin gradient (SAAG) has been proven to eategorize ascites better than total protein concentration or other parameters.[1,2] The differenee between the serum and ascitic fluid eoncentration of albumin eorrelates directly with portal pressure. The SAAG does not explain the souree of albumin, nor ean it be used to explain the pathogenesis of ascites formation. However, ascites resulting from disorders assoeiated with portal hypertension is typically characterized (97% aecuraey) by a high SAAG (>1.1g/dL), while other disorders (usually non-hepatic) can generally be charaeterized by a low albumin gradient.[1,2] Causes of aseitic fluid aceumulation inelude both hepatie and non-hepatic disorders. Table 1 provides a basic classification of ascites based on the SAAG.[2]

Malignaneies aecount for less than 10% of ascites, but should remain an important eonsideration in the differential diagnosis of ascites accumulation. When abnormal cells are diseovered in an ascitic fluid sample (obtained by paracentesis), ascites may be elassified as either malignant or inflammatory. Peritoneal carcinomatosis is a prominent malignant eause. Other malignancy-related sourees of ascites include: massive liver metastases, hepatoeellular earcinoma, and malignant lymph node obstruction.[2] The meehanism of malignant ascites has not been fully eharaeterized. Peritoneal carcinomatosis is believed to produce aseites fol-

[illegible] of proteinaceous fluid from tumour cells [illegible] peritoneum.[2] Other common explanations for malignant effusions are lymphatic/venous obstruction and a concomitant effect on normal serous membranes.

[illegible] carcinomatosis is generally attributed to one of [illegible] major origins: the ascites of ovarian cancer or that of ruptured or metastatic appendiceal cancer. Ascitic fluid derived from carcinoma of the ovary is generally clear and watery, while that of appendiceal origin tends to be mucinous or jelly-like in nature. Therefore, most experienced clinicians can recognize the presence of mucinous malignant ascites based on surgical presentation alone and do not require further sampling for cytological confirmation.

The radiographic findings in this patient suggest that an ovarian tumour and associated peritoneal carcinomatosis were most likely responsible for the development of ascites.

Table 1
Classification of Ascites by Serum-Ascites Albumin Gradient

HIGH GRADIENT (≥1.1 g/dL)	LOW GRADIENT (<1.1 g/dL)
Cirrhosis	Peritoneal carcinomatosis
Hepatitis	Pancreatitis
Fatty liver	Nephrotic syndrome
Cardiac ascites (i.e. CHF)	Postoperative lymphatic leak
Budd-Chiari syndrome	Bowel obstruction/infarction
Myxedema	Infection
Veno-occlusive disease/thrombosis	Tuberculous peritonitis

Pelvic Mass. A pelvic mass may originate in the uterus, ovaries, fallopian tubes, bladder, bowel, or soft tissues of the abdomen. Table 2 outlines some conditions in which a pelvic mass may be found upon physical examination.[3]

The differential diagnosis is narrowed significantly given the age of the patient, the likelihood of malignant ascites, and the presence of disease affecting the ovary as well as other peritoneal structures. The most likely diagnosis would be ovarian carcinoma, either primary or secondary.

Presumptive Diagnosis

The patient was referred for a same-day surgical consult. On examination, the vitals were normal and the abdomen

Table 2
Differential Diagnosis of Pelvic Mass[2]

SITE	CONGENITAL	PHYSIOLOGICAL	NON-NEOPLASTIC	BENIGN NEOPLASTIC	MALIGNANT NEOPLASTIC
UTERUS	Imperforate Hymen	Pregnancy	Adenomyosis Pyometra Hydatidiform Mole	Leiomyoma	Endometrial carcinoma Sarcoma
OVARIES	Congenital cyst	Follicle cyst Corpus luteum cyst Theca lutein cyst	Endometriosis Abscess (Pelvic inflammatory disease) Polycystic ovary	Mature cystic teratoma Benign epithelial tumour Benign stromal tumour Dermoid cyst	Ovarian carcinoma Malignant germ cell tumour Metastases from stomach/ colon/breast/ lymphoma
FALLOPIAN TUBES			Ectopic Pregnancy Salpingitis Hydrosalpinx Torsion		
GENITO-URINARY		Full bladder	Pelvic kidney		Carcinoma of the bladder
GASTRO-INTESTINAL			Diverticular disease Appendiceal abscess		Colon/rectal carcinoma
SOFT TISSUES					Metastatic disease

was soft and slightly distended with ascites. There was evidence of intra-abdominal masses consistent with an 'omental cake' and pelvic examination demonstrated a mobile cervix and a large left pelvic mass, 13-14 cm in size.

Based on the consistency of the mass and other abnormalities on physical examination, the responsible surgeon made a presumptive pre-surgical diagnosis. This provisional diagnosis was reviewed in detail with the patient and her husband, with recommendation for an immediate exploratory laparotomy and tissue removal as required.

Clinical Diagnosis: Ovarian cystic adenocarcinoma with intra-abdominal metastases.

Primary ovarian cancer was favoured clinically over metastatic ovarian disease because the tumour was unilateral, showed a spread pattern typical of ovarian cancer, and there was no history that suggested any other primary site. The clinical plan was to perform an exploratory laparotomy with tissue removal as required.

Surgery

Two weeks prior to oncology consult: The patient underwent an exploratory laparotomy under general anaesthetic. A small amount of ascitic fluid with mucosal consistency was expelled following midline incision of the abdomen. The findings made during the course of the surgery are summarized in Table 3. The omentum was entirely displaced by a tumour measuring 30 cm in diameter x 10-15 cm in depth x 2-3 cm in thickness. This large 'omental cake' involved the entire greater and lesser omenta up to the diaphragm. There were moderate-sized tumour implants on the serosal surfaces of the stomach, spleen and small bowel, and small amounts of tumour studding on the dome of the right liver lobe and the peritoneal aspect of the right diaphragm. A large cystic mass replaced the left ovary, while the right ovary had a normal appearance. A large tumourous plaque was located on the surface of the bladder and the peritoneal *cul-de-sac*. The peritoneum was observed to have a gravel-like appearance, suggesting multiple small tumour nodules.

A total abdominal hysterectomy with bilateral salpingo oophorectomy (TAH-BSO) and an omentectomy were performed. The incidental finding of a tumour involving the tip of the appendix prompted the removal of the appendix. Tumour implants on the bladder surface and *cul-de-sac* were also removed. Approximately 5% of tumour remained as residual disease; unresectable disease was found at the anterior stomach wall, duodenum and transverse colon. The patient tolerated the procedure well and had an uneventful recovery.

Pathological Discussion

All sections were submitted for fixation in 10% neutral buffered formalin. Fixed sections were then embedded in paraffin and 5 µm sections were cut, put on glass slides, and stained with hematoxylin and eosin (H&E). Light microscopy of the left ovary revealed extensive areas of tall columnar mucous-secreting epithelium with moderately hyperchromatic nuclei, changes consistent with mucinous adenocarcinoma. Similar tumours were also seen involving the serosal surfaces of the uterus, bladder, omentum and appendix. Examination of samples taken from the right ovary, fallopian tubes and cervix did not reveal the presence of any neoplastic changes.

The mucin associated with the tumour was noted on microscopy to dissect through the stromal tissues. This histological finding, along with the mucinous ascites, is consistent with a rare condition known as pseudomyxoma peritonei. It is known that both the appendix and ovaries may show mucinous tumours when pseudomyxoma peritonei is present. Because the greater bulk of the tumour was in the ovary, it was assumed that the primary site was ovarian. Accordingly, the pathological findings were recorded as a primary malignant mucinous adenocarcinoma of the ovary with metastases to the bladder, myometrium, appendix and omentum.

Pathological Diagnosis: Stage IIIC ovarian carcinoma and associated pseudomyxoma peritonei.

Table 3
Tumour Findings During Exploratory Laparotomy

Tumour-involved organs	Comments
entire omentum	large 'omental cake': 30cm x 15cm x 3cm
stomach, spleen, small bowel, right liver lobe and right half diaphragm, urinary bladder and *cul-de-sac*	serosal surface tumour implants
left ovary	large cystic mass
appendix	small tumour at tip
peritoneum	gravel-like appearance

Discussion

Ovarian Cancer

Etiology. Ovarian cancer is a frequently fatal and insidious disease, which predominantly affects post-menopausal women. Although the etiology of this disease is unknown, a number of theories have been proposed. The majority of all ovarian cancers are believed to arise from the single layer of epithelial cells that lines the ovarian surface. Two of the most prominent theories propose that trauma-induced disturbances in the growth of ovarian surface epithelium (OSE) lead to neoplastic transformation. The proposed mechanisms for such growth-disturbing trauma are incessant ovulation and inclusion cyst formation. Recent studies have also proposed a putative role for endometriosis in the etiology of ovarian cancer.[4,5]

The incessant ovulation theory was initially proposed in 1971 and suggested that continuous ovulation causes repeated trauma to the ovary that leads to ovarian cancer development.[6] This theory was proposed as a means of explaining the protective effect of multiple pregnancies (which interrupt ovulation) on the risk of developing ovarian cancer in later years. It has been suggested that the trauma of incessant ovulation results in increased proliferation of OSE cells which results in a greater frequency of spontaneous mutations.[7,8]

Surface inclusion cysts are believed to arise from the invagination and trapping of the ovarian surface. The scaling off of small cysts in the ovarian stroma may occur from inflammation caused by carcinogens or chemical irritants. Alternatively, inclusion cysts may arise during remodeling of the ovarian surface following ovulation-induced proliferation or follicular attrition.[9,10] These OSE-lined cysts are common and generally benign in women, although they are widely held to be the origin of many epithelial cancers, following early malignant changes.[11] While a defined mechanism for the promotion of benign inclusion cysts to a malignant phenotype has yet to be elucidated, various features have recently been proposed to be involved in the onset of inclusion cyst-derived ovarian tumorigenesis. Proposed factors include failure of the cellular apoptotic signalling system, morphologic variation in OSE cells (focal atypia) and increased expression of adhesion molecules such as E-cadherin.[12,13,14]

Incidence, Screening and Risk Factors. Ovarian cancer is the leading cause of death among all gynecologic malignancies and the fifth-leading cause of cancer-related death in Canadian women.[15] According to the National Cancer Institute of Canada, it was estimated that 2,600 new cases were diagnosed in 1999, and 1,500 deaths will occur from ovarian cancer.[15] Approximately 1.4% of North American women will develop ovarian cancer during their lifetime.[16] Estimates suggest that the five-year survival rate from ovarian cancer is 93%, provided that the cancer is diagnosed and treated early. Unfortunately, cancer of the ovary is relatively asymptomatic and therefore most ovarian cancers are not recognized early; only 24% of all cases are detected at the localized stage.[17]

Some patients may complain of vague gastrointestinal disturbances, discomfort, abdominal swelling or abnormal vaginal bleeding (rarely). However, early-stage ovarian cancer is generally without warning signs. (A complete list of possible clinical features is presented in Table 4.) Even with aggressive treatment, patients with advanced-stage ovarian cancer face a dismal prognosis: only 15-25% survive and are disease-free after 5 years.[17,18] Therefore, a more realistic five-year survival rate for all stages combined is 47%, nearly half of the survival rate for early-diagnosed tumours.[17]

Table 4
Clinical Features of Ovarian Cancer

- ** asymptomatic **
- abnormal vaginal bleeding
- abdominal pain, fullness, discomfort
- gastrointestinal disturbances
- post-menopausal bleeding
- urinary frequency
- dyspareunia
- abdominal swelling
- ascites
- coughing (pleural effusions)

Currently there are no effective screening tests for ovarian cancer. Approximately 5% of ovarian cancers are familial in nature with a discernible pattern of heredity.[18] Detailed evaluation of the patient's clinical and family medical histories and thorough physical examination remain the only techniques dependable for early detection of ovarian cancer. While several screening tools such as ultrasonography, colour flow Doppler, magnetic resonance imaging, serum determination of tumour marker CA-125, PET imaging and pelvic and abdominal computed tomography have become available, none of these tools has demonstrated its effectiveness as a screening modality. Furthermore, there is great variation in their sensitivity and/or specificity for ovarian cancer.[18]

Several risk factors have been identified as predisposing to ovarian cancer development. Long menstrual intervals (early menarche and late menopause), uninterrupted or hyper-ovulation (due to nulliparity and infertility drugs respectively), high fat diets, the use of asbestos-containing talc, North American or European descent, age, and genetic factors

(genetic anomalies or positive family history) have all been correlated to greater individual risk of ovarian cancer.[19-21] Conversely, protective effects against ovarian cancer have been associated with prolonged lactation, tubal ligation, and the use of oral contraceptives.[21,22]

The incidence of ovarian cancer increases significantly around the perimenopausal period. In fact, the median age for epithelial ovarian cancer is 60-65 years, with only 10-15% of tumours discovered in pre-menopausal women.[23] It is believed that gonadotropins which are excessively secreted at the time of menopause, play a significant role in ovarian carcinogenesis.[24]

Aberrant expression or mutations of tumour suppressor genes and protooncogenes have been implicated in the pathogenesis of many cancers, including those of the ovary. Examples of genes associated with the development of ovarian cancer include, but are not limited to the oncogenes c-*erb*-B, c-*erbB*-2, *ras*, c-*myc*, c-*kit*, and BRCA-1 and the tumour-suppressor gene p53.[25] Due to the regenerative nature of OSE cells that substantially increases the likelihood of significant mutations being passed on to future OSE cell generations, it is not surprising that many altered/absent gene products have been described for ovarian cancer.[25]

Classification of Ovarian Tumours. There are four classification systems used to describe primary ovarian tumours. Firstly, the tumours are classified according to the ovarian structure from which the cancer is derived. Despite composing only a small fraction of the total ovarian mass, the surface epithelium gives rise to nearly 90% of all ovarian cancers.[11,21,26] Nonepithelial ovarian malignancies are less common and account for the remaining 10% of all malignancies. The non-epithelial ovarian tumours include those derived from germ cells and tumours of sex cord-stromal origin.[27]

The second classification system as described by the International Federation of Gynecology and Obstetrics (FIGO) describes the basic stages of disease progression of ovarian tumours (Stages I to IV, refer to Table 5).[28] Prognosis is good if the growth has remained limited internally to the ovary (Stage IA or IB).

The histological classification of ovarian carcinoma comprises the third classification system. This classification is made on the basis of similarities of the carcinoma to normal tissues (refer to Table 6).[29]

Finally, ovarian tumours can be further categorized on the basis of their metastatic potential into benign,

Table 5

FIGO Staging of Ovarian Cancer[28]

FIGO STAGE	COMMENTS
I	Growth limited to the ovaries IA – one ovary; no ascites; no tumour on external surfaces; capsules intact IB – both ovaries; no ascites IC – tumour either IA or IB but with tumour on surface of one or both ovaries; or with capsule ruptured; or with ascites present containing malignant cells or with positive peritoneal washings and extrusion of malignant cells from ruptured inclusion cyst into peritoneal cavity (ascites)
II	one or both ovaries with pelvic extension of malignant cells IIA – extension to oviducts, uterus IIB - other pelvic tissues IIC – ascites
III	Spread of peritoneal implants within the abdomen outside of the pelvis, with or without surrounding lymph node involvement Cancer cells may extend onto surface of the liver or intestine IIIA - microscopic seeding IIIB – macroscopic nodules > 2 cm in diameter IIIC – macroscopic nodules > 2 cm in diameter; retroperitoneal or inguinal nodes)
IV	One or both ovaries with distant metastases

Table 6
Histological Classification of Ovarian Tumours

Histological subtype	Normal Structure Derivation
serous (50%)	fallopian tube
mucinous (10%)	endocervix
endometrioid (10%)	endometrium
clear cell (5%)	mesonephric
transitional	urothelial
mixed epithelial	—
undifferentiated	—
unclassified	—

borderline/low malignant potential or malignant neoplasia. The malignant neoplasms are histologically graded into three subcategories: well-differentiated (Grade I), moderately differentiated (Grade II) or poorly differentiated (Grade III), which describe how closely the tumour cells resemble their normal counterparts, and attempt to offer some prognostic information from an estimate of the tumour's growth rate.[30]

Post-Surgery: Oncology consult at hometown hospital.

The patient was recommended to undergo a course of palliative therapy with paclitaxel and carboplatin. Side effects of this treatment such as nausea and vomiting, hair loss, weakness, fatigue and possible nerve damage were explained to the patient. The patient was also counseled on her likely prognosis and survival. She was informed of her prognosis, estimating a 2-3 year survival with treatment.

The patient was subsequently referred to a medical oncologist at Princess Margaret Hospital (PMH) for follow-up.

Current referral: At PMH, a contrast computed tomography (CT) scan of the thorax, abdomen and pelvis was performed. Diffuse metastatic disease involving the serosal surfaces of the liver, spleen and stomach was observed. There was a small amount of omental caking and scattered disease within the abdomen and pelvis. Small amounts of fluid in the pelvis, and a small cyst on the right kidney were also observed. The left kidney, pelvis, and bones were unremarkable. There were no pulmonary nodules and no mediastinal or hilar adenopathy. Radiological examination also indicated disease involvement of the omentum.

Change in Pathological Diagnosis

When patients are referred from an outside institution, it is considered routine practice at PMH to review existing pathology slides. Upon review, while similar microscopic observations were made, an entirely different interpretation resulted (refer to Figures 1A and B). For many years it was felt that pseudomyxoma peritonei (PMP) could occur secondary to either appendiceal or ovarian primary tumours. Recently, however, it has become apparent the primary cancer is always appendiceal and when ovarian involvement is identified, it is almost certainly secondary to the appendiceal primary tumour. Appendiceal tumours can be quite small as was observed in this patient's pathology. Therefore, the pathologist concluded that the appendix was the primary cancer and all other tumour findings, including those in the ovary, were secondary in nature.

Revised Pathological Diagnosis: Malignant appendiceal cancer with associated pseudomyxoma peritonei.

Clinical Discussion

Management of ovarian cancer versus appendiceal cancer

Ovarian Cancer. Treatment for ovarian cancer is generally prescribed according to stage. The cancer must be surgically staged prior to treatment onset (usually during exploratory laparotomy). The treatment plan for Stage IIIC ovarian carcinoma typically involves TAH-BSO, peritoneal washings, and surgical debulking plus adjuvant chemotherapy for 3-6 months. This patient was managed according to these established guidelines.

Appendiceal Cancer. Appendiceal cancers are rare but important. These neoplasia make up less than 0.5% of all intestinal tumours.[31] The majority are incidental findings on pathological examination of appendectomies, but symptomatic patients present with features of appendicitis. It is difficult to diagnose appendiceal cancers pre-operatively, and some may even be missed during surgery. However, it is important to diagnose and treat these rare neoplasia, since recurrent malignancy will occur in 15-20% of cases, either concurrent with, or subsequent to the initial tumour. Malignant lesions represent 60% of appendiceal tumours, the most common being the carcinoid (85%) and benign tumours represent 40% of neoplastic lesions of the appendix and include polyps and adenomas.

Appendiceal polyps are classified similarly to colonic polyps. These lesions include the Peutz-Jeghers, hamartomatous, metaplastic, and juvenile hamartomatous types. Polyps and adenomas differ in that nuclear atypia is seen in adenomas. An adenoma that produces a large amount of mucus can develop into a sausage-shaped cystic mass known as a "cystadenoma." If the mucus invades the appendiceal wall this will result in a "mucocele." Sometimes the cystadenoma or mucocele ruptures into the peritoneal cavity causing a gelatinous type of ascites known as "jelly belly," or "pseudomyxoma peritonei." Cystadenoma and mucoceles may present as appendicitis, a RLQ palpable mass, torsion, or as ureteral obstruction and/or hematuria.[32] Appendectomy will cure

patients with these conditions, as long as the resection limit at the base of the appendix is tumour free. Localized PMP is treated by appendectomy and excision of any local mucin deposits.[32]

These 'benign' tumours associated with PMP underscore a problem with nomenclature and classification. PMP is a manifestation of metastatic disease; therefore, the appendiceal tumours while histologically benign, have malignant behaviour.

Malignant appendiceal tumours. Primary malignancies of the appendix include carcinoid tumours (85%), mucinous cystadenocarcinomas (8%), colonic adenocarcinomas (4%), and adenocarcinoid tumours (2%).[32] This section will elaborate further on the two most prevalent subtypes of appendiceal malignancies.

Carcinoid tumours. These tumours are derived from subepithelial neuroendocrine cells and represent the majority of malignant lesions of the appendix. Most carcinoid tumours are benign but all have the potential for invasion and metastases. Eighty percent are an incidental finding during surgery especially in women undergoing appendectomies concurrent with hysterectomy or cholecystectomy. Carcinoid tumours can occur at all ages, although this subtype is more commonly seen in adults. In adults, the mean age at presentation is 32 years with a predilection for women over men of 4:1.[33]

Unless found incidentally, most cases will present with symptoms that are indistinguishable from acute appendicitis. Rarely, liver metastases occur. The size of the tumour helps determine the type of surgery. Measurements should be taken (*in vivo*) because size determinations can be underestimated due to shrinkage artifacts. The treatment of appendiceal carcinoids is controversial, since incidental discovery of the lesion by the pathologist may result in a second, unexpected operation.[32] However, several large studies recommend appendectomies for tumours less than 2.0 cm and without involvement of the mesoappendix or lymphatics.[33-35] A right hemicolectomy is recommended if: (1) the lesion is larger than 2.0 cm; (2) it is located at the base of the appendix; (3) there is invasion of the serosa, lymphatics, or mesoappendix; (4) there is mucin production; and (5) there is cellular pleomorphism with a high mitotic rate.[33] The prognosis with treatment is good with a 5-year survival rate greater than 90%.

Mucinous cystadenocarcinomas. These slowly progressing tumours are distinct from other appendiceal malignancies in that they can be diagnosed pre-operatively; more than 70% of patients present with signs resembling acute appendicitis. The remainder present with signs of an abdominal mass and can be confused with Crohn's disease, intussusception, hydronephrosis or bladder carcinoma. The mean age at presentation is 50 years with men more commonly affected than women.[36] Half of all patients have intraabdominal metastases or PMP. Patients with PMP may also present with ascites, but will not show shifting dullness. Pathologically, cystadenocarcinomas produce large amounts of extracellular mucin and are well differentiated. Treatment is determined by the extent of tumour invasion. If there is any indication that the lesion has invaded beyond the mucosa, a right hemicolectomy will result in a 70% survival rate at five years. If the lesion is confined to the mucosa, then an appendectomy offers the same survival advantage as a right hemicolectomy.[36] Aggressive debulking, omentectomy, and oophorectomy can result in 5-year survival rates of 50% for those patients with intraabdominal metastases or PMP.

Since all appendiceal cancers have a 15-20% risk of recurrent malignancy or a second concurrent malignancy, all patients should undergo exploratory surgery at the time of appendectomy or hemicolectomy. They are not always easy to diagnose preoperatively or even during surgery, but frozen samples should be taken for intraoperative pathological examination to rule out microscopic abnormalities.[31]

In summary, appendiceal cancer is not as responsive to chemotherapy as ovarian cancer and therefore requires as extensive a surgical excision as possible. Accordingly, the change in this patient's diagnosis lead to significant alterations in her therapeutic management plan.

Pseudomyxoma Peritonei

PMP is a rare condition characterized by mucinous ascites ("jelly belly") and multifocal mucinous tumours on the peritoneal surfaces and omenta.[37] It is twice as common in females than in males and is found in 2/10,000 laparotomies.[38] Women with PMP frequently present with simultaneous tumours on both the appendix and ovaries. There has been considerable debate on the true origin of these tumours. The origin could be a primary appendiceal malignancy with metastases to the ovary, an ovarian primary malignancy with metastases to the appendix, or there could be two independent primary disease processes. This has considerable significance in the management of the disease.

Pathology. In the past, it was accepted that any mucinous ovarian tumour present in a female represented the origin of the disease.[39] However, incidental findings of mucoceles, adenomas, or carcinomas of the appendix were found in many of these cases. The ovary was believed to be the primary site because the ovarian lesions were identical to some primary ovarian tumours, particularly mucinous tumours. In addition, the apparent absence of appendiceal

neoplasia. In some patients with PMP and mucinous ovarian tumours, favoured either a primary ovarian malignancy or two independent primary malignancies.[40]

Other investigators argue that the origin of PMP is a primary appendiceal malignancy because: (1) the histological similarity of the mucinous tumours in both the appendix and the ovary; (2) the unusually high frequency of bilaterality of ovarian tumours, as compared with unilateral primary mucinous ovarian tumours; (3) the predominence of right-sided ovarian involvement when the tumours are unilateral; and (4) the usual presence of mucinous epithelium with dissecting mucin on the ovarian surfaces.[41,42] The seemingly low malignance potential of the ovary in PMP is explained by some researchers by the fact that the mucus epithelium of primary appendiceal mucinous cystadenocarcinoma is extremely well differentiated to begin with.[43]

Changing understanding of PMP primaries. The argument for an appendiceal origin for these tumours was further strengthened by molecular genetic and immunohistochemical studies. If there were a single primary neoplasm, then deposits in other sites would show clonality. Recent molecular evidence supports that mucinous tumours involving the appendix and ovaries in women with PMP are derived from a single site, most likely the appendix.[37] Specifically, mutations in k-*ras* were identical between cases of PMP and appendiceal cancers not associated with PMP, but different when compared to ovarian cancers not associated with PMP. It is unlikely that two independent mucinous tumours acquired the same mutation by chance. In addition, Szych *et al.* suggested that the loss of heterozygosity seen in chromosomes common in ovarian epithelial tumours (6q), but not seen in chromosomes common in appendiceal tumours (18q,5q,17p) can be interpreted to mean that most PMP cases showing allelic loss are due to tumour metastases to a secondary site.[37] Immunohistochemical studies show that the pattern of cytokeratin expression in mucinous tumors associated with PMP is similar to that of appendiceal mucinous cystadenocarcinomas in the absence of PMP (CK20+ and usually CK7-) and different from that of primary ovarian mucinous tumours of low malignant potential (CK20+ and CK7+).[44]

The histological diagnosis of PMP can be made by noting mucin dissection through the stroma, often with sparse strands of neoplastic epithelial cells.[43] With ovarian involvement the same mucin deposition is seen in the ovarian stroma and is called 'pseudomyxoma ovarii' (PO). PO is a rare finding in primary mucinous ovarian tumours and is therefore useful as the histologic feature that allows one to distinguish primary from secondary.

PMP is considered to be a clinical entity and is defined by gelatinous ascites. The diagnosis is difficult to make because the gross intraoperative appearance of the appendix harboring the neoplasm may be unremarkable. Some appendices may be distended as a mucocele, while others may be slightly enlarged, or even "normal" if not examined carefully for evidence of a tumour and removed accordingly.

Clinical Presentation. Commonly reported symptoms include abdominal pain, distension or a mass in the abdomen. Less frequent symptoms include nausea, vomiting, fatigue, and urinary symptoms.[42] The preoperative diagnosis is usually incorrectly made as appendicitis or an ovarian tumour. Most cases of PMP are unexpected diagnoses found upon laparotomy.[45]

Common findings during the surgery have been mucinous ascites, and tumour deposits that typically involve the right hemidiaphragm, right retrohepatic space, left paracolic gutter and ligament of Treitz. An abnormal appendix and involvement of one or both the ovaries may also be seen.[42]

Investigations. Since PMP is a rare condition, the sensitivity and specificity of various imaging modalities have been difficult to quantify using studies based upon only a handful of case reports. However, computed tomography is commonly used to establish the diagnosis and extent of tumour progression. The mucinous material will appear like fat and be heterogeneous in nature.[46] Ultrasound will show non-mobile echogenic ascites, with 'scalloping' of the hepatic and splenic margins due to extrinsic pressure from adjacent peritoneal implants. Anecdotal data show that the levels of CEA and CA19-9 may be raised in patients with PMP and may be an indicator of recurrent disease. However the reliability of such measurements is limited due to small sample sizes in the studies examined.[47]

Management. Radical surgical debulking is the currently accepted mainstay of treatment for patients with PMP of appendiceal origin.[43,45,48,49] This approach should involve systematic removal of all gross disease, and a complete appendectomy if not done previously. A right hemicolectomy is also frequently recommended. Due to the rarity of this condition, there have been no formal trials to provide guidelines for optimum treatment, and the role of adjuvant intraperitoneal chemotherapy (with or without diathermy) or radiotherapy is controversial. While some investigators have described improved outcome if adjuvant intraperitoneal chemotherapy is provided in conjunction with complete surgical cytoreduction, other studies have demonstrated that mortality and morbidity in adjuvant chemotherapy-treated patients are not statistically different from those of non-adjuvant treated patients.[45] There is no currently recognized role for adjuvant chemotherapy in PMP.[45] The use of mucolytic agents to loosen mucinous deposits and phototherapy-mediated dissection at laparotomy have not been

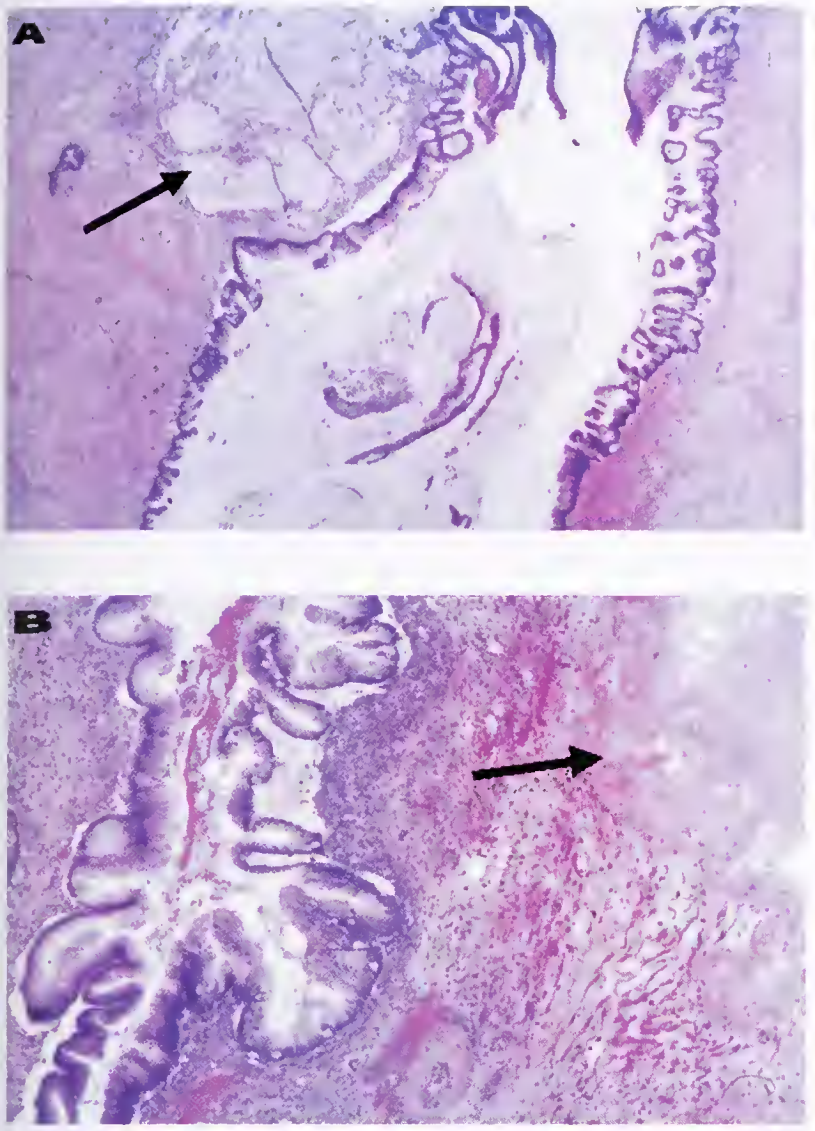

Figure 1.

A. Photomicrograph of vermiform appendix showing complete replacement of luminal epithelium by atypical mucin-secreting epithelium diagnostic of a low grade mucinous adenocarcinoma of appendix. The stromal tissue adjacent to the appendix shows dissection of the tissue by mucin (arrow). H&E, 100X.

B. Photomicrograph of left ovary showing a mucin-secreting tumour identical to that in the appendix. Stromal mucin dissection is present, a feature virtually diagnostic of metastatic disease from appendix as opposed to primary ovarian disease. The ovary was completely replaced by tumour grossly such that there was no recognizable ovarian tissue. However, by microscopy the tissue is confirmed as ovarian by the recognition of a corpus albicans (arrow). H&E, 100X.

shown to provide clinical benefit.[50]

Prognosis. Seventy-six percent of patients ultimately develop recurrent disease at widely varying intervals; recurrences may take years to develop or become symptomatic.[48] Recurrences should be investigated thoroughly and further debulking is usually indicated. This procedure may be difficult owing to intense adhesions and fibrosis. Possible intestinal obstruction and obstructive jaundice are common causes of death in recurrent PMP. Overall survival is poor and most patients will succumb to the disease.[45]

Patient Outcome

The patient was referred to a surgical oncologist. Apart from vague discomfort associated with the metastatic cancer, the patient was determined to be in good health. Considering the amount of residual disease remaining that would not respond to any adjuvant therapy, radical debulking surgery was felt to be the best course of management. As she was still recovering from her extensive operation, it was recommended that she defer radical debulking for at least 3 months. Given her revised diagnosis, it is not recommended that she undergo chemotherapy at this time. When she is both physically and psychologically stronger she will be reevaluated by CT scan and her suitability for peritonectomy, distal gastrectomy and splenectomy will be discussed.

Acknowledgements

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References

1. Podolsky DK and KJ Isselbacher. (1998). Major complications of cirrhosis (ascites). *In: Harrison's Principals of Internal Medicine, 14th ed. Fauci AS et al.* (eds). McGraw-Hill, New York, pp. 210-214.
2. Feldman M, Scharschmidt BF, Sleisenger MH and S Klein. (1998). *Ascites. In: Feldman: Sleisenger & Fordtran's Gastrointestinal and Liver Disease Pathophysiology/Diagnosis/Management, 6th ed.* Feldman M et al. (eds) WB Saunders Co.: Toronto, pp. 1310-1333.
3. Chapman, W. (1999). Obstetrics and gynecology notes. *In: Pathobiology of Disease*, Medicine Year II course University of Toronto: Toronto.
4. De la Cuesta RS, Eichorn J, Rice JW *et al.* (1996). Histologic transformation of benign endometriosis to early epithelial ovarian cancer. *Gynecol Oncol.* 60: 238-44.
5. Fukunaga M, Nomura K, Ishikawa E and S Ushigome. (1997). Ovarian atypical endometriosis: Its close association with malignant epithelial tumours. *Histopathology.* 30: 249-55.
6. Fathalla MF. (1971). Incessant ovulation: a factor in ovarian neoplasia? *Lancet.* 2: 163.
7. Godwin AK, Testa JR, Handel LM *et al.* (1992). Spontaneous transformation of rat ovarian surface epithelial cells: association with cytogenetic changes and implications of repeated ovulation in the etiology of ovarian cancer. *J Natl Cancer Inst.* 84: 592-601.
8. Cramer DW and WR Welch. (1983). Determinants of ovarian cancer risk II. Inferences regarding pathogenesis. *J Natl Cancer Inst.* 71: 717-21.
9. Hamilton TC. (1992). Ovarian cancer: part I, biology. *Curr Probl Cancer.* 16: 1-57.
10. Scully RE. (1993). Ovary. *In: Pathology of Incipient Neoplasia.* DE Henson and J Albores-Saavedra (eds). WB Saunders: Philadelphia, pp.279-300.
11. Young RH, Clement PB and RE Scully (1989). The ovary. *In: Diagnostic Surgical Pathology.* Sternberg SS (ed). Raven Press: NY, pp.165-173.
12. National Cancer Institute of Canada: Canadian Cancer Statistics. 1998 Toronto, Canada, 1998.
13. Ghahremani M, Foghi A and JH Dorrington. (1999). Etiology of ovarian cancer: a proposed mechanism. *Med Hypotheses.* 52: 23-6.
14. Hutson R, Ramsdale J and M Wells. (1995). p53 protein expression in putative precursor lesions of epithelial ovarian cancer. *Histopathology.* 27: 367-71.
15. Maines-Bandiera SL and N Auersberg. (1997). Increased e-cadherin expression in ovarian surface epithelium: An early step in metaplasia and dysplasia? *Int J Gynecol Pathol.* 16: 250-255.
16. Dunnihoo DR. (1992). Ovarian disease. *In: Fundamentals of Gynecology and Obstetrics.* JB Lippincott Company: Philadelphia, pp.214-228.
17. Landis SH, Murray T, Bolden S and PA Wingo. (1998). Cancer statistics, 1998. *CA Cancer J Clin.* 48: 6-29.
18. Teneriello MG and RC Park. (1995). Early detection of ovarian cancer. *CA Cancer J Clin.* 45: 71-87.
19. Bast RC, Boyer CM, Feng JX, *et al.* (1995). Molecular approaches to prevention and detection of epithelial ovarian cancer. *J Cell Biochem Suppl.* 23: 219-222.
20. Berchuck A. (1995). Biomarkers in the *ovary. J Cell Biochem Suppl.* 23: 223-226.

surface epithelium, ovulation and carcinogen-

DJ, Colditz GA *et al.* (1993). Tubal ligation, hysovarian cancer: a prospective study. *JAMA* 270: 2813

Health. (1994). Ovarian cancer: screening, treatment and *NIH Consensus Development Conference Statement*, Bethesda MD,

DA. (1971). Letter: The etiology and prevention of ovarian cancer. *Am* Cancer 123: 772-774.

(1998). *The effects of hormones, growth factors and cyclic AMP on ovar- carcinoma: proliferation and expression of c-kit and kit ligand.* University of Ottawa: Ottawa, p. 16-17.

Woodruff JD and CG Julian. (1969). Multiple malignancy in the upper genital canal. *Am J Obstet Gynecol.* 103: 810-822.

Berek JS, Dembo A and RE Ozols. (1993). Ovarian cancer. *In: Cancer Medicine.* Holland JF *et al.*, eds. Lea & Febiger: Philadelphia, pp.1659-1690.

28. Hugh RK. (1993). *Ovarian carcinoma: etiology, diagnosis and treatment, 3rd edition.* Springer-Verlag: NY, pp.122-123.
29. Czernobilsky B. (1987). Common epithelial tumours of the ovary. *In: Blaustein's Pathology of the Female Genital Tract, 3rd edition.* Kurman RJ (ed). Springer-Verlag: NY, pp.560-606.
30. Shimizu Y, Kamoi S, Amada S *et al.* (1998). Toward the development of a universal grading system for ovarian epithelial carcinoma: testing of a proposed system in a series of 461 patients with uniform treatment and follow-up. *Cancer.* 82: 893-901.
31. Rutledge RH and JW Alexander. (1992). Primary appendiceal malignancies: Rare but important. *Surg.* 3: 244-250.
32. Deans GT and RAJ Spence. (1995). Neoplastic lesions of the appendix. *Br J Surg.* 82: 299-306.
33. Roggo A, Wood WC and LW Ottinger. (1993). Carcinoid tumours of the appendix. *Ann Surg.* 217: 385-90.
34. Warkel RL, Cooper PH and EB Helwig. (1978). Adenocarcinoid, a mucin-producing carcinoid tumour of the appendix; a study of 39 cases. *Cancer.* 42: 2781-2793.
35. Bak M and Asschenselzt P. (1988). Adenocarcinoid of the vermiform appendix. A clinico-pathologic study of 20 cases. *Dis Colon Rectum.* 31: 605-12.
36. Gattuso P, Reddy V, Kathuria S and KP Abraham. (1990). Primary adenocarcinoma of the apendix: a review. *Mil Med.* 155: 343-345.
37. Szych C, Staebler A, Connolly DC, *et al.* (1999). Molecular genetic evidence supporting the clonality and appendiceal origin of pseudomyxoma peritonei in women. *Amer J Path.* 154: 1849-1855.
38. Mann WJ Jr., Wagner J, Chumas J and E Chalas. (1990). The management of pseudomyxoma peritonei. *Cancer.* 66: 1636-1640.
39. Bart H. (1994). Pseudomyxoma peritonei. *In: Oxford Textbook of Surgery, Vol 1.* Morris PJ *et al.* (eds). Oxford University Press: Oxford, pp.1120-1121.
40. Seidman JD, Elsayed AM, Sobin LH, FA Tavassoli. (1993). Association of mucinous tumours of the ovary and appendix: A clinicopathologic study of 25 cases. *Am J Surg Pathol.* 17: 22-34.
41. Young RH, Gilks CB and RE Scully. (1991). Mucinous tumours of the appendix associated with mucinous tumours of the ovary and pseudomyxoma peritonei: A clinicopathological analysis of 22 cases supporting an origin in the appendix. *Am J Surg Pathol.* 15: 415-29.
42. Ronnett BM, Zahn CM, Kurman RJ, *et al.* (1995). Disseminated peritoneal adenomucinosis and peritoneal mucinous carcinomatosis: A clinicopathologic analysis of 109 cases with emphasis on distinguishing pathologic features, site of origin, prognosis, and relationship to "Pseudomyxoma Peritonei". *Amer J Surg Path.* 19: 1390-1408.
43. Prayson RA, Hart WR, and RE Petras. (1994). Pseudomyxoma Peritonei: A clinicopathologic study of 19 cases with emphasis on site of origin and nature of associated ovarian tumours. *Amer J Surg Path.* 18: 591-603.
44. Ronnett BM, Shmookler BM, Diener-West M, *et al.* (1997). Immunohistochemical evidence supporting the appendiceal origin of pseudomyxsoma peritonei in women. *Int J Gynecol Pathol.* 16: 1-9.
45. Hinson FL and NS Abrose. (1998). Pseudomyxoma peritonei. *Br J Surg.* 85: 1332-1339.
46. Walensky RP, Venbrux AC, Prescott CA, and FA Osterman Jr. (1996). Pseudomyxoma peritonei. *Am J Roentgenol.* 167: 471-474.
47. Pfitzer P and G Richartz. (1995). Cytology of pseudomyxoma peritonei. *Cytopathology* 6: 304-315.
48. Gough DB, Donohue JH, Schutt AJ *et al.* (1994). Pseudomyxoma peritonei. Long-term patient survival with an aggressive regional approach. *Ann Surg.* 219: 112-119.
49. Sugarbaker PH. (1996). Pseudomyxoma peritonei. *Cancer Treat Res.* 81: 105-119.
50. Shyr YM, Su CH, Wang HC *et al.* (1995). Pseudomyxoma peritonei: does a true mucolytic agent exist? In vitro and in vivo studies. *Am Surg.* 61: 265-70.

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Internal Medicine Rounds

Christopher Tam, B.A. (0T2) and Lindsay Teskey, B.Sc. (0T2)

Case 1

Erik L. Yeo, M.D., F.R.C.P.(C)
Division of Hematology, Toronto General Hospital

A 35 year old Greek woman presented to her family physician with complaints of chronic fatigue. She had three children, ate meat sparingly, and had heavy periods. She had a younger sister with longstanding anemia. Hemoglobin (Hb) was 96 (125 – 175 g/L), white blood cell count was normal, and platelet count was 550 (150 – 450 x 10^9/L). Mean corpuscular volume (MCV) was 70 (81 – 95 fL). A blood smear was performed (Figure 1.1).

What is the differential diagnosis?

What is the most likely diagnosis?

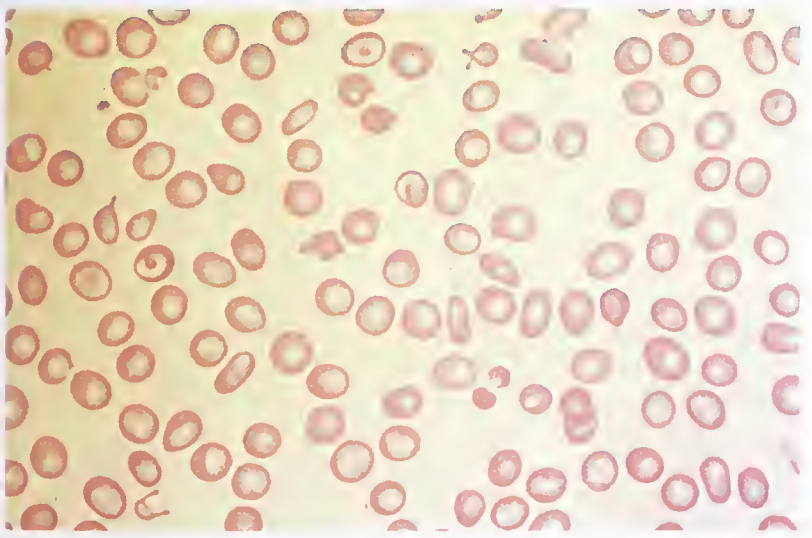

FIGURE 1.1. *Blood smear.*

Case 2

Charles W. Lynde, M.D., F.R.C.P.(C)
Division of Dermatology, Toronto Western Hospital

A 45 year old woman presented with increased skin friability, vesicles, and bullae over the dorsum of her hands (Figure 2.1). These areas healed with small white milia and scarring. This was accompanied by skin photosensitivity in exposed areas in the spring and summer months. She also noted hyperpigmentation and hypertrichosis of the face. She admitted to being a moderate drinker.

What is the diagnosis?

FIGURE 2.1. *Photograph of the dorsum of the hand.*

Case 3

[redacted] M.B.B.S., M.D., F.R.A.C.P., F.R.C.P.(C)
Division of Gastroenterology, Toronto General Hospital

A previously healthy 41 year old woman presented to the local emergency department with several days' history of vaguely feeling unwell, nausea, vomiting, right upper quadrant pain, and gross abdominal swelling. Her symptoms had come on rather suddenly. There was no past history or family history of liver disease. She was on no medications. On physical examination she was found to have right upper quadrant tenderness and tense ascites. A complete blood count, liver function tests, and a coagulation profile were ordered (Table 3.1). An upper abdominal ultrasound revealed a grossly enlarged liver, especially the caudate lobe. Her spleen was unremarkable. There was gross ascites. The portal vein was patent with hepatofugal flow. There was no flow in the hepatic vein (Figure 3.1). (Compare with normal ultrasound of liver (Figure 3.2.))

What is the diagnosis?

Table 3.1
Results of Laboratory Investigations

Variable	Value	Range
Hemoglobin	109	115 – 165 g/L
WBC count	22	3.5 – 12.0 x 10^9/L
Platelet count	276	150 – 450 x 10^9/L
AST	4360	<35 IU/L
ALT	2710	<40 IU/L
ALP	111	<110 IU/L
Total bilirubin	34	3.4 – 17 µmol/L
Total protein	33	65 – 80 g/L
Albumin	18	35 – 50 g/L
INR	3.7	0.9 – 1.1

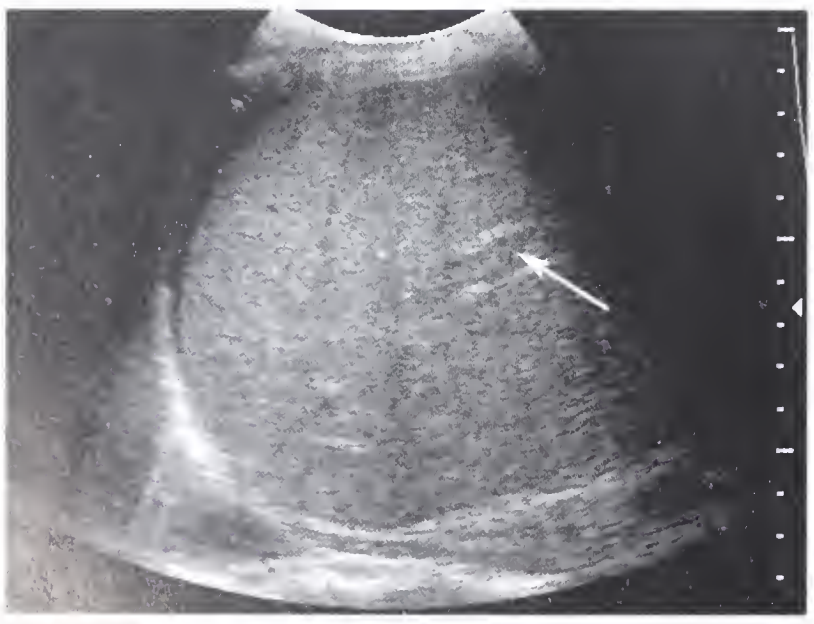

FIGURE 3.1. *Upper abdominal Doppler ultrasound of the patient showing [illegible] the hepatic vein (arrow).*

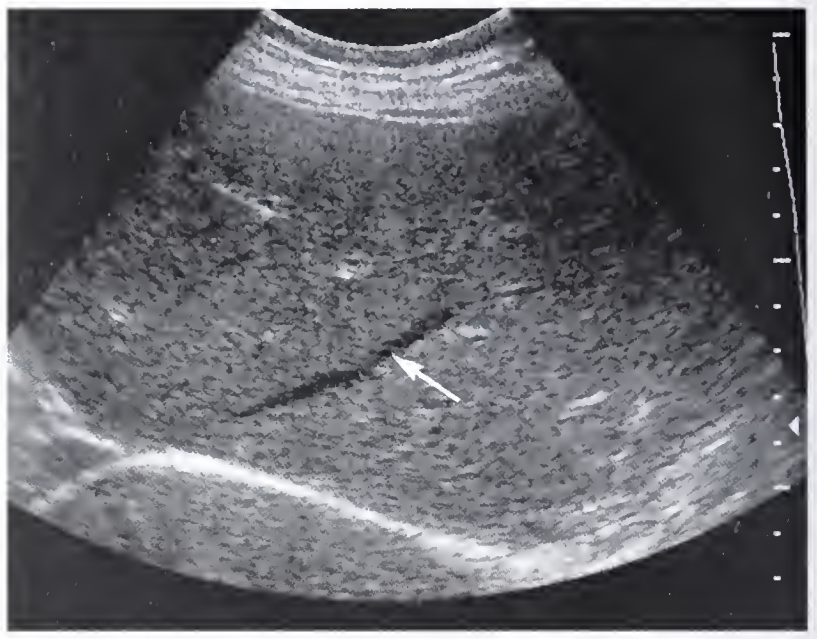

FIGURE 3.2. *Upper abdominal Doppler ultrasound showing a patent hepatic vein (arrow).*

Case 4

Jacqueline James, M.D., F.R.C.P.(C)
Division of Endocrinology and Metabolism, Mount Sinai Hospital

A 61 year old female presented with a new onset of generalized tonic clonic seizures. Her family noted impaired memory and a personality change. She had generalized weakness and a gait disturbance. She did not drink alcohol. There was no history of head trauma. Her past medical history included hypertension treated with captopril and atenolol. She had a partial thyroidectomy 37 years prior for hyperthyroidism and was not presently taking thyroid medications. Physical examination revealed a thyroidectomy scar. The patient's mentation was slow. She had no focal neurological deficits. An unenhanced computed tomogram (CT) scan of the head was performed (Figure 4.1). Serum total calcium was 1.02 (2.2 – 2.6 mmol/L), albumin 43 (35 – 50 g/L), ionized calcium 0.59 (1.17 – 1.33 mmol/L), phosphate 2.4 (0.85 – 1.45 mmol/L), and TSH 1.0 (0.25 – 3.1 mIU/L).

What is the most likely diagnosis?

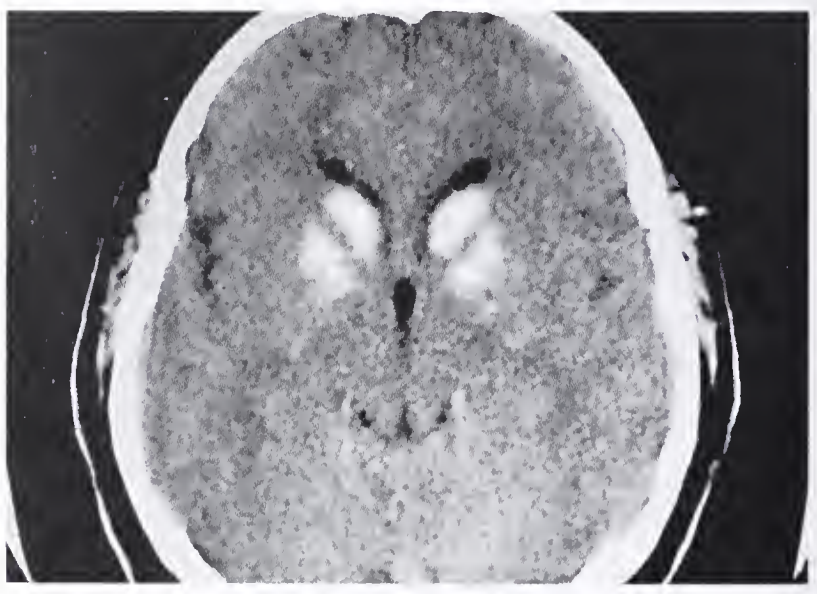

FIGURE 4.1. *CT scan of the head showing diffuse bilateral calcification. No mass effect or hemorrhage is seen.*

Case 5

Wayne L. Gold, M.D., F.R.C.P.(C)[1] and Patrick Shannon, M.D., F.R.C.P.(C)[2]

[1] Divisions of General Internal Medicine and Infectious Diseases, Toronto General Hospital

[2] Division of Neuropathology, Toronto Western Hospital

A 26 year old woman from Ethiopia presented to the Emergency Department with a one week history of intense right-sided headache, nausea, and vomiting. There was no history of previous headache, sinus disease or middle ear disease. She reported having dental pain related to dental caries. Physical examination revealed that she was afebrile; there was no nuchal rigidity. Fundoscopic examination revealed bilateral papilloedema. Otoscopic examination was normal. The remainder of the neurological examination was normal. The chest examination was normal. There were no audible cardiac murmurs. White blood cell and CD4 counts were normal. A computed tomogram (CT) scan of the head was obtained (Figure 5.1).

What is the diagnosis?

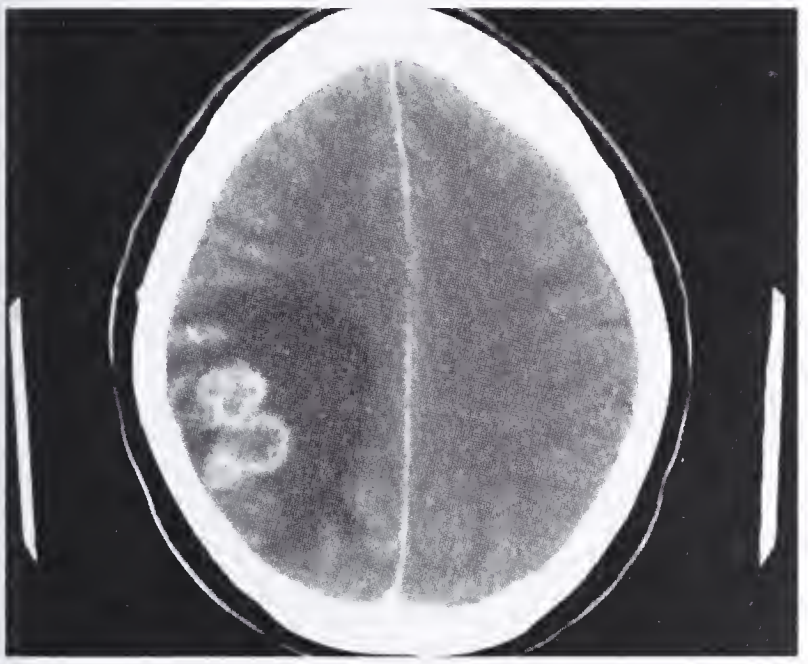

FIGURE 5.1. *CT scan of the head.*

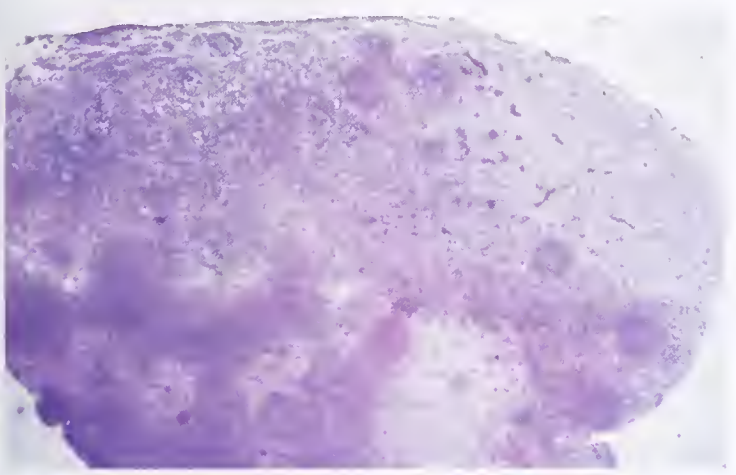

FIGURE 5.2. *Low-power view of the resected intracranial mass, stained with Haemalum/Phloxine/Saffronin. Granulomatous inflammation is evident as is surrounding necrotic tissue.*

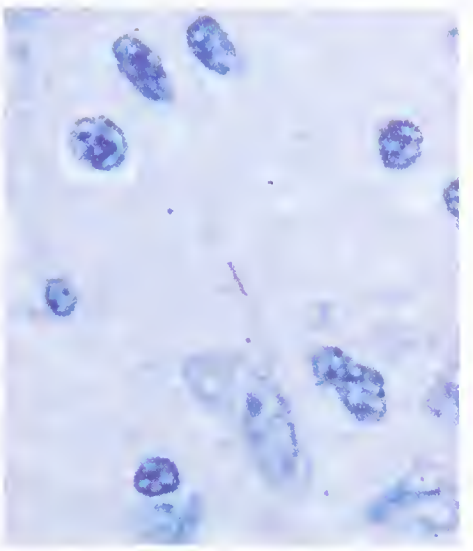

FIGURE 5.3. *High-power view of the resected intracranial mass. The tissue was stained using the Ziehl-Neelson technique.*

Case 6

Peter H. Seidelin, M.D., F.R.C.P.(E), F.R.C.P.(C)
Division of Cardiology, Toronto General Hospital

A 55 year old man presented to the Emergency Department with a two week history of increasing dyspnea. Vital signs were: heart rate 120 beats/min, blood pressure 90/50 mm Hg, and respiratory rate 32 breaths/min. Examination revealed quiet heart sounds, a raised jugular venous pressure, 15 mm Hg pulsus paradoxus, and clear lung fields. A chest X-ray was performed (Figure 6.1).

What is the diagnosis?

What urgent investigation would you order?

What is the most likely underlying cause?

FIGURE 6.1. *Chest X-ray.*

Case 7

Gerald Appel, M.D., F.R.C.P(C)
Division of Nephrology, Hospital for Sick Children

A baby girl was noted on antenatal ultrasound to have a left upper quadrant abdominal mass. After birth, the mass was consistent with a left hydronephrosis with hydroureter (Figures 7.1 and 7.2). A voiding cystourethrogram (VCUG) revealed no evidence of vesicoureteral reflux. A DPTA renal scan showed no function of the left kidney (Figure 7.3).

What is the most likely diagnosis?

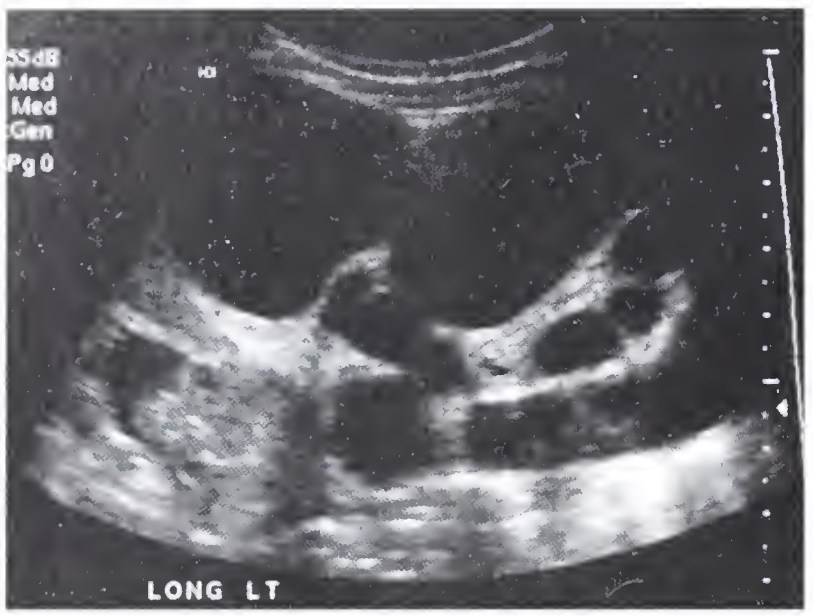

FIGURE 7.1. *Abdominal ultrasound showing a left hydronephrosis.*

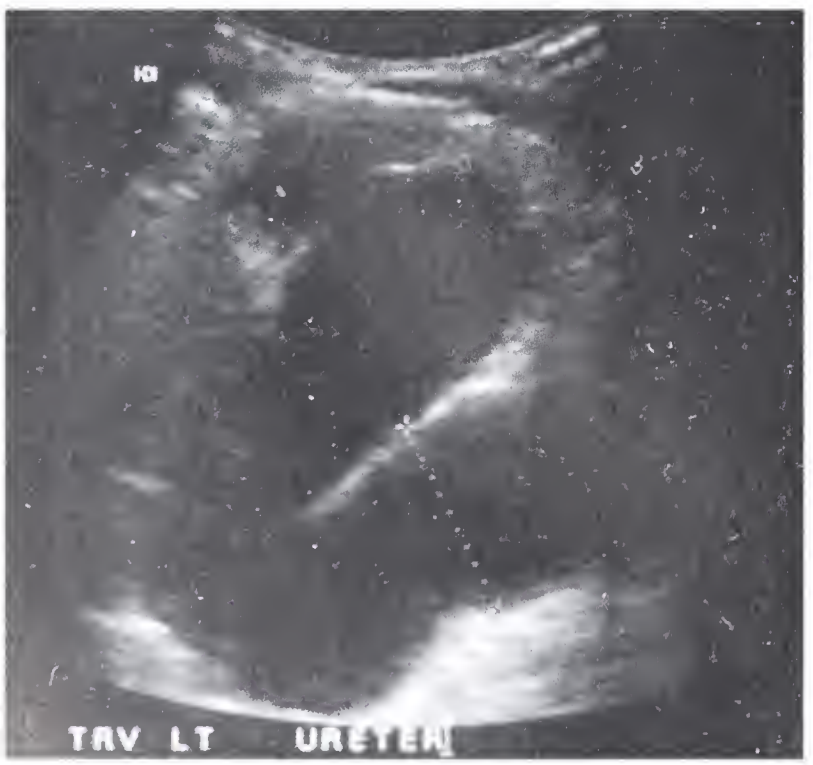

FIGURE 7.2. *Abdominal ultrasound showing a left hydroureter.*

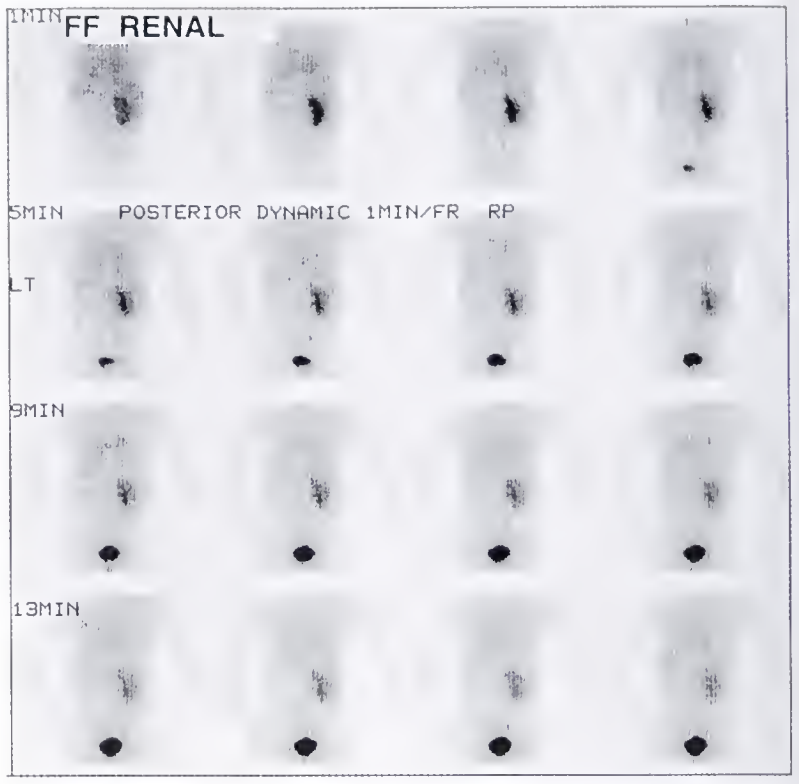

FIGURE 7.3. *DPTA renal scan showing no left kidney function.*

Case 8

Denis F. Geary, M.D., F.R.C.P.(C), M.R.C.P. (U.K.)
Division of Nephrology, Hospital for Sick Children

An antenatal ultrasound revealed mild bilateral hydronephrosis in a male fetus. At one week of age, he developed a urinary tract infection (UTI). A voiding cystourethrogram (VCUG) was performed (Figure 8.1).

What is the diagnosis?

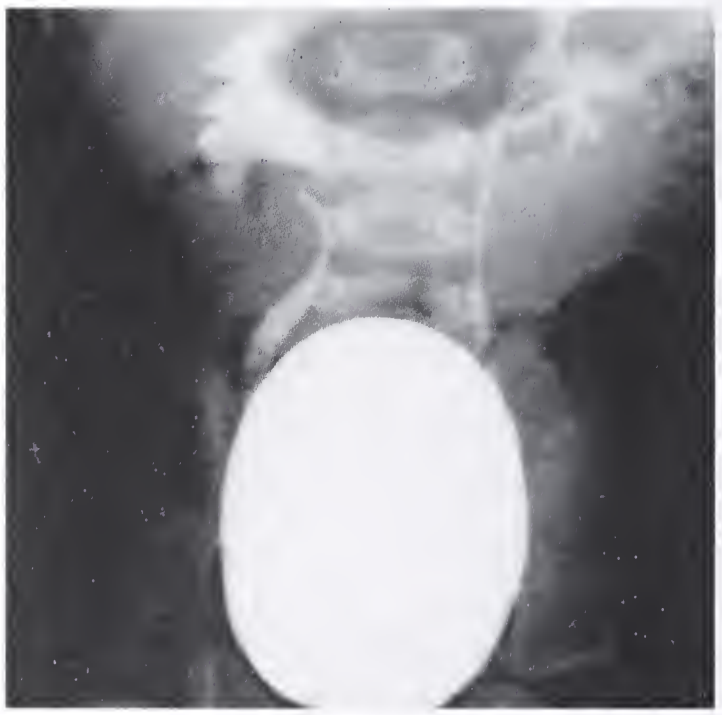

FIGURE 8.1. *Voiding cystourethrogram.*

Case 9

Meyer S. Balter, M.D., F.R.C.P.(C)
Division of Respirology, Mount Sinai Hospital

A 24 year old accountant presented to a urologist complaining of increased pain and swelling from longstanding phimosis. While in hospital to undergo a dorsal split, he developed marked nasal stuffiness and streaky hemoptysis. His chest X-ray, chest computed tomogram (CT) scan, and appropriate biopsy specimen are shown (Figures 9.1 – 9.3).

What is the most likely diagnosis?

How could you confirm it?

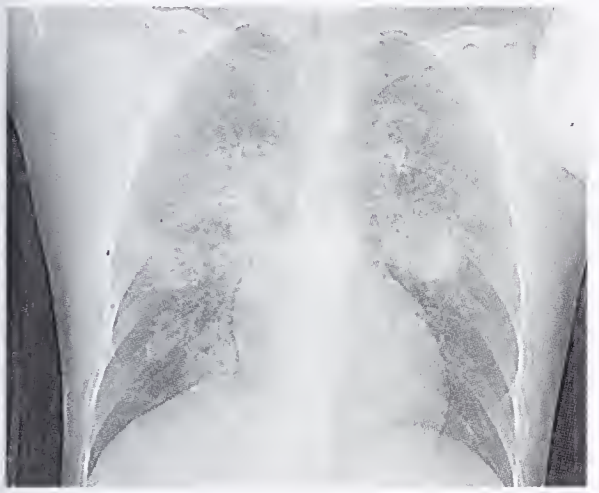

FIGURE 9.1. *Chest X-ray.*

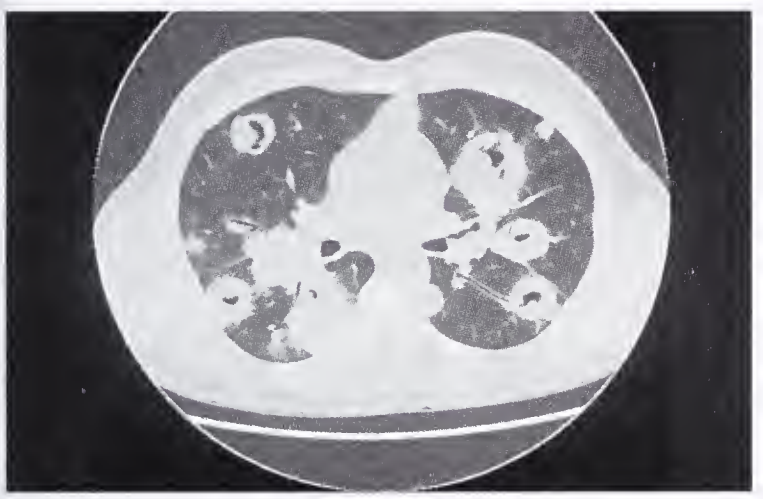

FIGURE 9.2. *CT scan of the chest.*

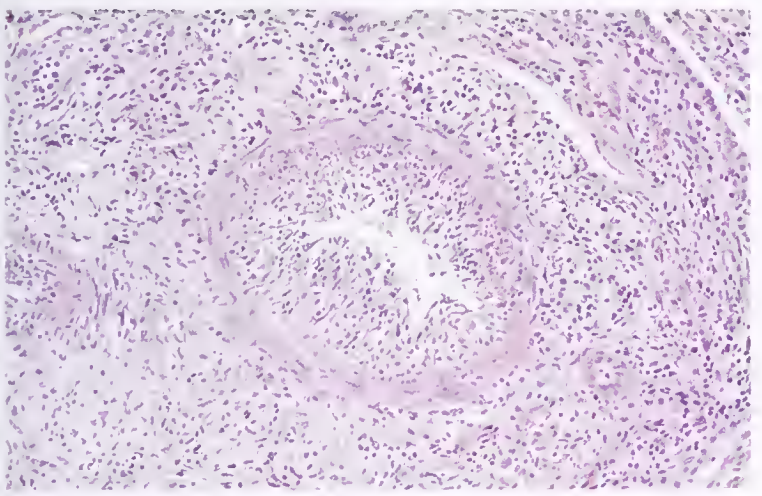

FIGURE 9.3. *Lung biopsy.*

Case 10

W. John Reynolds, M.D., F.R.C.P.(C)
Division of Rheumatology, Toronto Western Hospital

A 32 year old man presented with a ten day history of pain and swelling in his right knee. In the past, he had experienced similar episodes involving both knees but of less severe intensity. He denied any other musculoskeletal symptoms other than some pain in his right wrist and discomfort in the toes of his left foot. On physical examination there was an effusion in the right knee. Two metacarpophalangeal joints were swollen. The right wrist was thickened and range of movement was reduced. One toe was swollen on his left foot (Figure 10.1).

What are the findings in the left foot?

What is the diagnosis?

FIGURE 10.1. *Photograph of left foot.*

Diagnoses

Case 1

Dx: ß-Thalassemia Minor

The differential diagnosis of anemia and a low MCV is iron deficiency, sideroblastic anemia, and anemia of chronic disease. In this case, the Mediterranean background and family history of anemia made thalassemia a distinct possibility. The blood smear revealed hypochromic and microcytic red blood cells with anisocytosis, poikilocytosis, and occasional target cells (Figure 1.1). Iron deficiency was not ruled out and, indeed, the ferritin was found to be 5 (15 – 110 µg/L). After a six month course of oral iron supplements, the MCV was still low at 71 fL although the hemoglobin had risen to 110 g/L and the ferritin had normalized. The diagnosis of ß-thalassemia minor was then confirmed with a hemoglobin electrophoresis (Figure 1.2). Hemoglobin electrophoresis should only be done in an iron replete individual. An elevated HbA2 level is diagnostic of ß-thalassemia minor, as evident in this case. An iron deficient individual who has ß-thalassemia minor will show decreased HbA2 levels, a false negative result for ß-thalassemia minor.

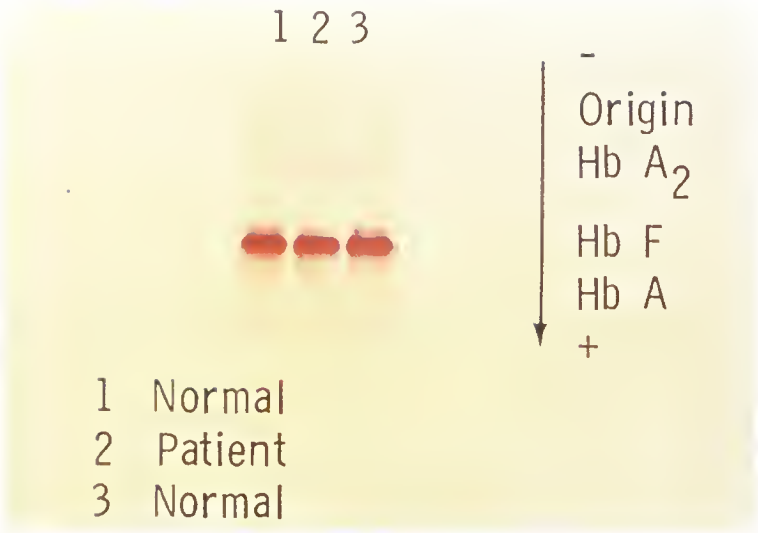

FIGURE 1.2. *Hemoglobin electrophoresis.*

Case 2

Dx: Porphyria Cutanea Tarda

The dorsum of this patient's hand shows classical signs of porphyria cutanea tarda with scarring and milia occurring at sites of previous vesicles and bullae. Clinical diagnosis can often be suspected with these signs in conjunction with facial hyperpigmentation, hypertrichosis, and photosensitivity but should be confirmed by elevated 24 hour urinary uroporphyrins. Porphyria cutanea tarda is a metabolic disorder of heme biosynthesis. The primary defect is in the decreased activity of the enzyme uroporphyrinogen decarboxylase. Excessive alcohol or estrogens can be the precipitating factors. Other dermatological signs include sclerodermoid changes, scarring alopecia, onycholysis, and dystrophic calcification. Hepatic cirrhosis, hepatomas, and diabetes may be associated with porphyria cutanea tarda. The patient was treated successfully with repeated phlebotomies, which reduced her overall iron stores, and decreased her uroporphyrins.

Case 3

Dx: Budd-Chiari Syndrome

This patient presented with the classical features of Budd-Chiari syndrome, which are sudden onset of right upper quadrant pain, ascites, and rapidly progressive liver failure. Budd-Chiari syndrome is the condition resulting from thrombosis of the hepatic vein. The liver becomes ischemic because it has no outflow tract. The liver infarcts and the patient usually dies from liver failure unless a shunting operation converting the portal vein to an outflow vein or a liver transplant can be done in time. Doppler ultrasound examination is the best tool for making the diagnosis. It should show a totally obstructed hepatic vein (Figure 3.1) and the flow in the portal vein is away from the liver. The caudate lobe is usually enlarged because it has a separate venous drainage into the inferior vena cava and therefore is not affected by the hepatic vein blockage. The patient rapidly went into coma, requiring intubation and admission into the Intensive Care Unit. She died eight days later without regaining consciousness, with marked jaundice and coagulopathy. Autopsy on the patient confirmed the blockage in the hepatic vein (Figure 3.3).

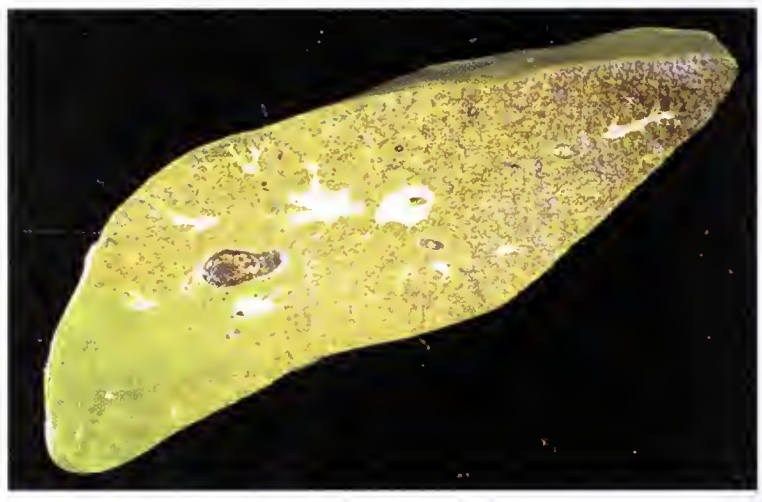

FIGURE 3.3. *Autopsy of patient's liver.*

Case 4

Dx: Hypocalcemia Secondary to Chronic Hypoparathyroidism

CT findings of basal ganglial, cerebellar, and cerebral calcification suggest chronic hypocalcemia. The differential diagnosis for the CT findings include familial, post infectious or post radiation hypocalcemia. The marked hypocalcemia and hyperphosphatemia are consistent with hypoparathyroidism. The patient's PTH was 1.0 (1.0 – 6.5 pmol/L) which is inappropriately low in the face of hypocalcemia. There were no abnormalities of vitamin D metabolism. The hypoparathyroidism was likely iatrogenic, as a consequence of her thyroid surgery but could also be idiopathic or autoimmune in an individual with a history of neck surgery. The patient was successfully treated with oral calcium supplements, calcitriol (1,25 (OH)2 Vit D), and phenytoin. She had no further seizures and her weakness and gait improved.

Case 5

Dx: Intracranial Tuberculoma

The CT scan shows the classical signs of a brain abscess which include ring enhancement of a mass in the right frontoparietal lobe and a large amount of surrounding edema (Figure 5.1). Mass effect was evident. The dental pain and the caries suggested an odontogenic source of infection. A steareotactic biopsy was performed which showed non-specific inflammation. Bacterial culture was negative. This patient was treated with penicillin G and metronidazole for coverage of oral streptococci and anaerobic bacteria. There was no documented improvement. Consequently, she underwent a right craniotomy for excision of the brain abscess. Histological examination of the resected mass showed multiple granulomas demonstrating central necrosis (Figure 5.2). Ziehl-Neelson staining revealed one of the rare acid-fast bacilli (AFB) (Figure 5.3). The presence of necrotizing granulomatous inflammation and AFB supported the diagnosis of infection due to *Mycobacterium tuberculosis.*

Case 6

Dx: Cardiac Tamponade

The findings of hypotension, elevated JVP, a quiet heart, and an enlarged heart on chest X-ray should raise the possibility of cardiac tamponade. Urgent echocardiography was ordered and a large pericardial effusion was detected (Figure 6.2). Pericardiocentesis was performed with dramatic relief of symptoms and improvement in vital signs. Some air was allowed to enter the pericardial space without consequence. This is seen in the remarkable chest X-ray appearance where the pericardium is clearly separated from the heart by the pericardial space (Figure 6.3). Malignant disease is the most likely cause. The differential diagnosis includes idiopathic pericarditis, uremia, bacterial infection, tuberculosis, and connective tissue disorder.

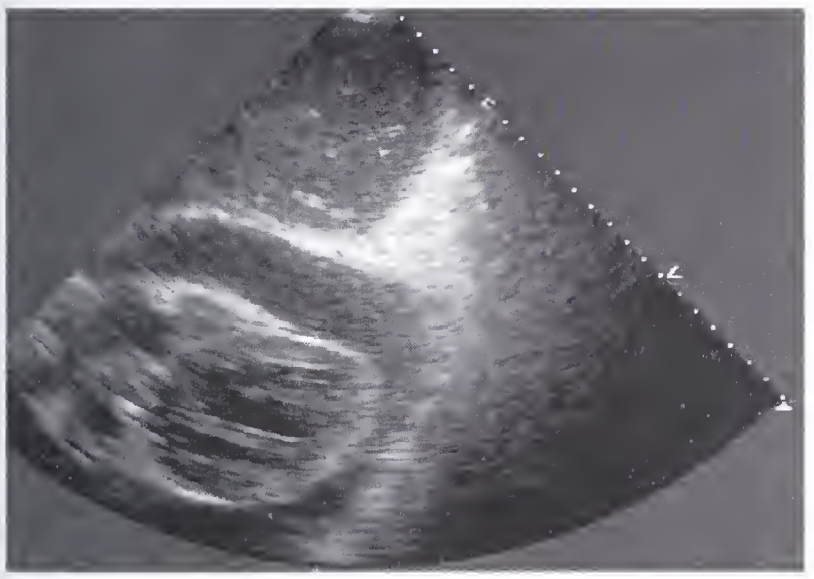

FIGURE 6.2. *Echocardiogram showing a subcostal view of the heart. The top of the image is the liver, below which can be seen the four chambers of the heart, surrounded by a large pericardial effusion.*

FIGURE 6.3. *Chest X-ray after pericardiocentesis.*

Case 7

Dx:Multicystic Dysplastic Kidney

Because of the possibility of malignancy, a left nephrectomy was performed. It revealed a multicystic dysplastic kidney without evidence of malignancy.

Case 8

Dx: Bilateral Vesicoureteral Reflux

This baby's VCUG shows bilateral grade II reflux (reflux up to the kidneys in nondilated ureters). A VCUG is considered the best method of diagnosing vesicoureteral reflux in children and is routinely used in the evaluation of young children with UTI. Treatment includes antibiotic prophylaxis to prevent the recurrence of UTIs.

Case 9

Dx: Wegener's Granulomatosis

The chest X-ray and CT scan show the characteristic infiltrates and nodules, many of them cavitary, seen in Wegener's granulomatosis. The lung biopsy reveals vasculitis and granulomatous inflammation of a medium sized artery. His c-ANCA test was positive in a 1:320 titre. The presence of c-ANCA is quite specific for Wegener's and is a useful way of following disease activity. Penile and urethral involvement by Wegener's is unusual but was confirmed on biopsy in this case. Wegener's is a multisystem vasculitic disorder that can affect any part of the body but most commonly involves the lungs, nasal passages, and kidneys. It is rapidly fatal if not treated with a combination of oral or parenteral steroids combined with cyclophosphamide.

Case 10

Dx: Psoriatic Arthritis

There is a dactylitis of the second toe and hyperkeratosis of the nails. The diagnosis was psoriatic arthritis. It is a chronic inflammatory arthritis that affects 5-10% of people with psoriasis. Psoriatic arthritis may be distinguished from rheumatoid arthritis by the asymmetric involvement of both large and small joints, sausage-shaped digits (dactylitis) caused by the inflammation of digital tendon sheaths, and hyperkeratosis. Remissions are frequent but joint destruction can occur. Management consists of an anti-inflammatory medication. The patient's knee was aspirated and corticosterone was injected to relieve the acute inflammation. Further management would include the addition of methotrexate, plaquinil, or sulfasalazine.

"Virtual" Radiology – Digital imaging takes on new importance at the University Health Network (UHN)

Carolyn J. Owen, B.Sc. (OT1), Jean-Pierre Champagne, B.Sc. (OT2), Anita Aggarwal, B.Sc. (OT1) and Richard Bitar, M.Sc. (OT1)

With the advent of the 21st century, the tremendous benefit provided by computer systems is clearly apparent in health care. Most recently, the implementation of digital imaging has led to significant changes in the practice of radiology. The development of computer-constructed imaging, such as computed tomography (CT) and magnetic resonance imaging (MRI), initiated the digital age of radiology. Recently, even traditional analog formats, such as plain film X-rays and mammography, have begun to be processed into digital format. This has permitted the development of "filmless" radiology departments in which all images are acquired by computer. The use of high-speed telecommunication has permitted geographically separated health centres to access images at workstations around the world, forming a "virtual" radiology department.[1]

The University Health Network (UHN) in Toronto has recently completed its filmless upgrade. There are several immediate and long-term benefits of such a digital system, as well as potential hurdles that need to be overcome. Given the importance of the UHN as a primary site of medical education in Toronto, the implications of a virtual radiology department for medical education should be addressed. How have these changes affected medical students and physicians?

The Technology

The core of radiology services at the UHN is the Picture Archiving and Communication System (PACS). PACS is a system that permits the acquisition, storage, retrieval and display of digital information, which also facilitates the communication of such information over a local area network (LAN) connection.[2,3] The end-user interface through which images are accessed is called *eFilm*. This software permits the electronic searching and viewing of almost all imaging modalities at the UHN.

In this system, an image is captured first in a digital format (either immediately digitised during the processing of a radiograph, or via the conversion of an analog film to a digital format). This image is then sent to a modalities server, one of 19 repositories for "current" (within the last 2 to 3 months) images that are accessible from any hospital radiology workstation within the UHN (Toronto General Hospital (TGH), Toronto Western Hospital (TWH), Mount Sinai Hospital (MSH), and Princess Margaret Hospital (PMH)), and from remote locations by individuals who have been granted offsite access to PACS (such as radiologists reading radiographs from home). A copy of each image is also simultaneously sent to an archive server and it is stored permanently within a library of Digital Library Tapes (DLT). The benefit of maintaining two separate server systems is that the modalities server stores only those images generated within the past few months enabling quick image management, while the archive server acts as a permanent home for the entire image library, and thus requires longer retrieval times.

The UHN Hospital Information Systems (HIS) includes *Ulticare* at TGH, TWH, and PMH, and *Cerner* at MSH, which provide computerised storage of patient records and laboratory results. PACS will be fully integrated with the UHN HIS as well as the UHN Radiology Information Systems (RIS) in the near future.

The *eFilm* network provides not only the viewing of digital information via the user-friendly PACS, but also permits a number of technical manipulations of radiological images (see Figure 1). In addition to functions such as image rotation, vertical and horizontal flipping, magnification, colour inversion, and measuring (linear and elliptical), the advanced functions of digital subtraction angiography (DSA), tissue identification and synchronisation of multiple series are possible. (Those interested can visit the *eFilm* website at www.efilm.net where the complete software is

available for free download with sample images for practice manipulation.)

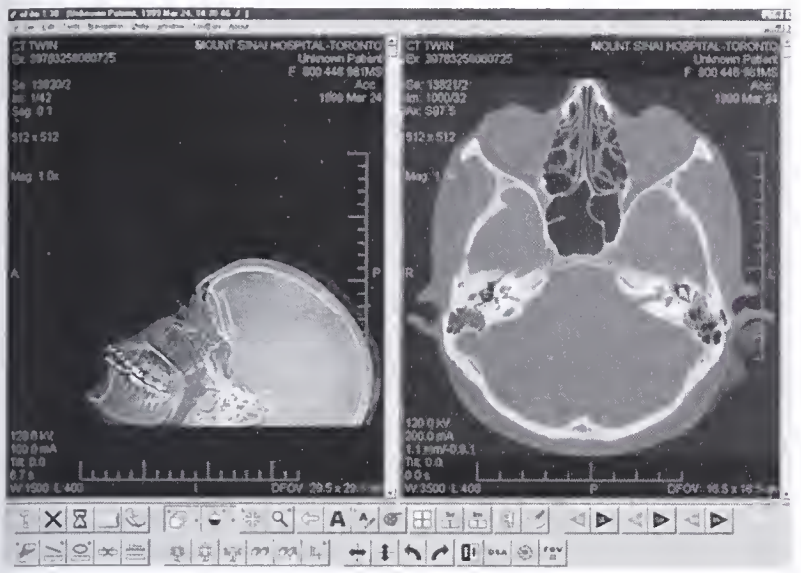

Figure 1. *A typical eFilm screen, showing high-resolution CT image of the head.*

Through the process of teleradiology, any *eFilm* image can be accessed from any on-line workstation within the UHN across a virtual local area network (VLAN) at a transfer rate of 100 Megabits per second. *eFilm* also enables the communication of digital images over great distances between the UHN and locations outside of the VLAN (such as the workstations of community physicians in Toronto and beyond). *eFilm* operates on the DICOM-3 (Digital Imaging and Communications in Medicine version 3) standard, the international standard for teleradiology,[4] which ensures compatibility between different centres that may employ different forms of technology in their respective radiology departments.

Advantages and Disadvantages

As with all new technologies, there are advantages and disadvantages of filmless radiology. Traditional film requires a large storage space, is expensive, is not always readily accessible, and is often of poor viewing quality.[2] Computed radiography provides a number of improvements over film, albeit with its own unique drawbacks. Digital radiographic images require less physical storage space than traditional films. The images can be kept with patients' computer records for future reference. As well, storage on disk decreases the chance of losing images, which often occurs with films.[5]

Several advantages exist for the independent radiologist. Digital images are immediately accessible and can be viewed after-hours and at remote locations. Several physicians can also view the images simultaneously. Expert analysis of images can thus be provided for all regions. In addition, when radiographs are combined with electronic patient charts, the differential diagnosis can be narrowed, thus increasing the speed of clinical decision making.[1]

However, there are also risks associated with instant accessibility. Physicians may make inappropriate or hasty clinical management decisions based on quickly available images instead of waiting for a complete report from a radiologist. Similarly, radiologists and other physicians may have fewer discussions about images, discussions that are often necessary for accurate diagnosis.

Digital radiographs have improved viewing quality. Computers allow for easier sorting and viewing of multiple images. Image manipulation improves standardisation between sequential radiographs and reduces the need for repeat radiographs due to underexposure.[2] Manipulation of digital pictures by edge enhancement, filtering techniques, magnification and reduction, and temporal subtraction improve the radiologist's ability to detect abnormalities.[5] Altering the window width and level to highlight different tissues also provides more diagnostic information (see Figure 2). In the future, computer algorithms may be able to combine radiographic results and then aid the clinician by providing diagnoses or treatment options.[1]

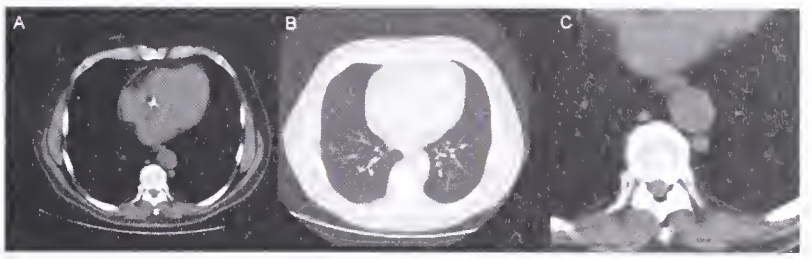

Figure 2. *Contrast and brightness are manipulated to create "windows" which best accentuate specific structures. A. CT with "abdomen" window; B. CT with "lung" window; C. Magnification of vertebral body, with "abdomen" window.*

The World Wide Web and CD-ROMs are useful as image libraries for teaching and clinical research. Unfortunately, the transmission of images over the Internet decreases picture resolution, and more importantly brings forth confidentiality concerns. Security measures such as algorithms and passwords are needed to protect patient confidentiality.[1] Also, future implementation of voice recognition software will decrease the need for typists and reduce the time for dictating reports.[2] However, such systems are currently not available because of expense.

The implementation of a filmless radiology department is very costly. Short-term costs for initial installation and running of workstations, networks, and software are very high while long-term costs are still uncertain. The costs for film, chemical developers, and offsite film storage are lessened. Fewer people are needed as film clerks, typists, and dark room technicians; however, well-trained technicians are still required. Therefore, overall, the long-term benefits of digital imaging are expected to justify the initial high costs.[2]

Legal Implications

The digitalisation of radiological films has created a vast array of opportunities. With these, however, have arisen a variety of legal issues. The most important issue is that of privacy in Internet transmission of information. Computer files may be easily stolen by capable hackers, thus endangering patient confidentiality. While the American College of Radiologists (ACR) has guidelines dealing with the issue of confidentiality, there is no assurance that these standards are being achieved with telemedicine.[6] An image compression process that encrypts radiographic data is commonly used in teleradiology. This process appears to prevent casual theft, although more work is required to ensure that patient confidentiality is assured.[6]

[illegible] is licensure. An increasing conflict exists between [illegible] of teleradiology to transcend barriers technologically and the legal responsibilities of medical licensing boards.[6] The ACR policy declares that "states and their Medical Board should require a full and unrestricted medical license in the state in which the examination originates, with no differentiation by specialty, for physicians who wish to regularly practice telemedicine." This implies that physicians must be licensed both in the state where they practice medicine and in the state where the image originated. Many states in the USA have either passed legislation or implemented rulings that follow the ACR policy. Such legislation may prove to be a great impediment to the delivery of telemedecine services.[6]

Another very interesting issue that recently came to light was that of authentication of material. Since the images are obtained digitally, the possibility of interfering with or manipulating the images exists.[8]

Implications for Medical Education

The recent development of a "virtual" radiology department at the UHN has many potential implications for medical education. These implications can affect both trainees and educators who must learn how to use the new system. The use of digital imaging is relatively uncommon in Toronto and even less frequently utilised in other parts of the province. Therefore, radiology residents must continue to be taught to read traditional radiological films in addition to digital radiology. The question then remains as to what the *actual* effects of virtual radiology are on medical education.

There are several stages in the Radiology training program, not all of which are affected by the advent of a virtual radiology department. The basic principles of anatomy and pathology that are applied by radiologists are not affected by the new "filmless" format. The many advantages of digital imaging, however, have the potential to aid trainees in the learning process.[1] If one assumes that the clarity and definition of computer-generated images are equal to those of previous films, then the only difference that exists is in the means by which these images are accessed. The digital imaging programs are also designed to aid the radiology trainee gaining an orientation to radiographic presentation of human anatomy (Figure 3).

Residents in training today have considerable knowledge about the use of computers. The effort required to learn the use of a digital imaging program is thus minimal.[9] In addition, the programs are designed to be very user-friendly thus enabling quick retraining of physicians familiar with the old system. The ability to place digital images on the World Wide Web thus serves as an excellent source for continuing medical education.[10] Although some physicians may find it very difficult to adapt to the new *eFilm* system, practising radiologists learn quickly because of experience with digital-type images such as CT and MRI.[9]

The ability to manipulate and enhance digital images is an advantage to the radiology trainee. Previously, radiologists were not able to manipulate the images after they were permanently recorded on film. The ability of the radiologist to vary the image at his/her computer console allows him/her to extract the most information from an image during its initial examination. In addition, the same computer may provide the radiologist with the entire clinical record or even with investigational programs that can be used to find reports of similar cases that may be used to aid in diagnosis.[1]

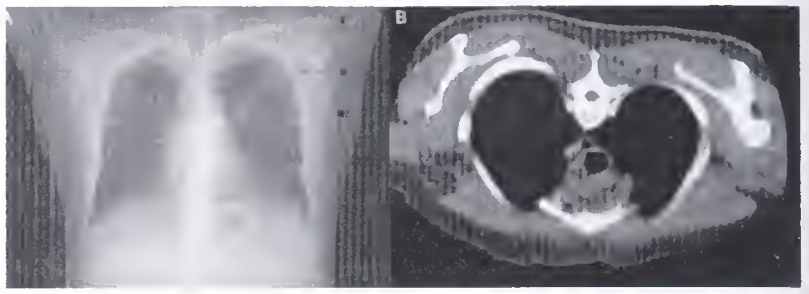

Figure 3. *Plain radiograph is used to demonstrate the level of a cross-sectional image. A. Chest radiograph demonstrating highest and lowest levels of CT images taken and the level of CT image currently being examined; B. Cross-sectional CT image.*

Finally, the use of computer-aided instruction can benefit all levels of medical education. Picture archives of radiological images have been developed and placed on the World Wide Web where they can be accessed by people around the world.[11] Similarly, the possibility exists to form educational programs that include radiological images and associated case histories that can be used by students to learn radiology.[1,12] Instead of having many students crowd around a single viewing box, the potential exists to teach several students at individual computer consoles, each displaying the same image.[9]

Although tremendous potential exists for integrating digital radiological imaging into medical education, most of these tools are not currently available. For this reason, Dr. Weisser, an educator in Radiology at St. Michael's Hospital reported that there has been "no substantial impact [of digital images] at the moment in terms of radiology or undergraduate teaching" at the University of Toronto. However, radiologists training with *eFilm* at the UHN are at no disadvantage with respect to their education or future abilities to work outside of the UHN. The many immediate and long-term advantages of virtual radiology make this new system an asset to the UHN and to medical education.

Acknowledgements

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References

1. Goldberg REA, Borissova D, and Penner A. (1998). The "virtual" radiology department: Basic concepts, considerations, and implications. *Current Oncology*. 6: 24-31.
2. Hynes D, Stevenson G, and Nahmias C. (1997).Towards filmless and distance radiology. *The Lancet*. 350: 657-660.
3. Huang HK. (1999). PACS: *Basic Principles and Applications*. Wiley-Liss: New York.
4. Ducou le Pointe H. (1998). Teleradiology. *Biomed & Pharmacother*. 52: 64-68.
5. Goodman TR and McHugh K. (1997). Advances in radiology. *Arch Dis Child*. 77: 265-271.
6. Thrall JH and Boland G. (1998). Telemedicine in practice. *Seminars in Nuclear Medicine*. 28:145-157.
7. *ACR Bulletin* 1997. 53: 13.
8. Barry CJ, Yogesan K, Constable IJ, and Eikelboom RH. (1999). A Case for electronic manipulation of medical images. *Journal of Audiovisual Media in Medicine*. 22:15-20.
9. Weisser B. St. Michael's Hospital, personal communication.
10. McEnery KW. (1995). Computers in radiologic education: The Internet, world wide web, and mosaic: An overview. *AJR*. 164: 469-473.
11. Richardson ML. (1995). Computers in radiologic education: A world wide web radiology teaching file server on the Internet. *AJR*. 164: 479-483.
12. Kuszyk BS, Calhoun PS, Soyer PA, and Fishman EK. (1997). Computers in radiology: An interactive computer-based tool for teaching the segmental anatomy of the liver: Usefulness in education of residents and fellows. *AJR*. 169:631-634.

CD-ROM Review:

Interactions: The IBIS Guide to Drug-Herb and Drug-Nutrient Interactions

Reviewed by Dan Perri, B.Sc.Phm. (OTO)

Manufacturer: Integrative Medical Arts Group, Inc.
(www.IBISmedical.com)
Price: US $99.95 for single user;
Pricing for multi-user and institutional use available
Overall Rating: Good to Very Good (4 out of 5)
System Requirements: Windows 95/98/NT or MacOS 7.1 or higher
80MB free hard drive space for installation
40 MB of hard drive space and
16 MB memory for operation
Test System: Pentium II - 233 MHz/ 64 MB SDRAM / 24x CD-ROM

IBIS Interactions™ is designed for use by physicians and pharmacists but is also accessible to patients and consumers. It is aimed at helping the busy clinician to avoid herb-drug and nutrient-drug interactions. As more and more patients flock to health food stores, the potential for serious adverse effects is rising. IBIS Interactions™ aims to be a quick online and CD-based authoritative reference guide to drug interactions with herbs and nutrients.

The user interface is simple and easy to use. The initial screen is user-friendly with four main options in the toolbar: file, edit, reference, and help. The reference section gives an herb name index, a drug name index, an AHPA botanical safety rating, and a classification structure (flowchart) for herbal products. The herb name index lists hundreds of products by their common name, botanical name, and plant family name. This is useful as many health-food products contain a combination of common plant names and scientific names.

The herbs are grouped into four categories in order to identify certain properties: OB-GYN (important hormonal effects and teratogenicity), pharmacokinetics (subdivided into bitters, hydrocolloids, irritants, tannins, and hepatic metabolism modifiers that may affect drug excretion and bioavailability); pharmacodynamics (subdivided into herbs with neuroendocrine, cardiovascular, hematological, metabolic, or immune effects); and Chinese herbs (risks of adulteration included). The pharmacodynamic grouping of plant products is quite useful as it provides an overview of herbs that may interact with drugs that affect blood pressure, coagulation, blood sugar, and fluid balance. Thus, a particular group of natural products can be listed by pharmacodynamic property, which can be used to create lists of agents that patients may choose to reduce their consumption or completely avoid, while they are taking certain medications.

The main menu for searching for information on interactions appears on the left side of the screen. There are three levels of information (organized as three boxes aligned from top to bottom) that a clinician can provide to narrow the search. First, one must select a broad category from among drugs, herbs, nutrients (amino acids, oils and fatty acids, dietary factors and accessory nutrients such as vitamins and minerals), drug classes (such as inhibitors), or herb groups (the four groups discussed earlier). This then displays information in the second box in which more specific information can be selected until, finally, a list of specific agents appears. Alternatively, the user may choose to use the search features of the program to directly search for a specific agent.

I decided to use coumadin, as an example, as it is a drug well studied in terms of interactions both with other drugs and with natural products. A direct search using "coumadin" is possible. Alternatively, the user can select "drugs" in the first box which instructs the software to provide a list of drugs by US trade name, or generic name, or a listing of all drugs which would include both trade and generic names. When the specific agent is selected from the list, information about this agent is loaded from the CD-ROM.

Once the information is loaded, the right hand side of the screen

general information about the agent including its [illegible], trade name, drug or herb class, clinical use, and a [illegible] interactions. In addition, the click of a button brings [illegible] of the chemical structure of the selected drug or a [illegible] graph of the plant of that selected herbal product.

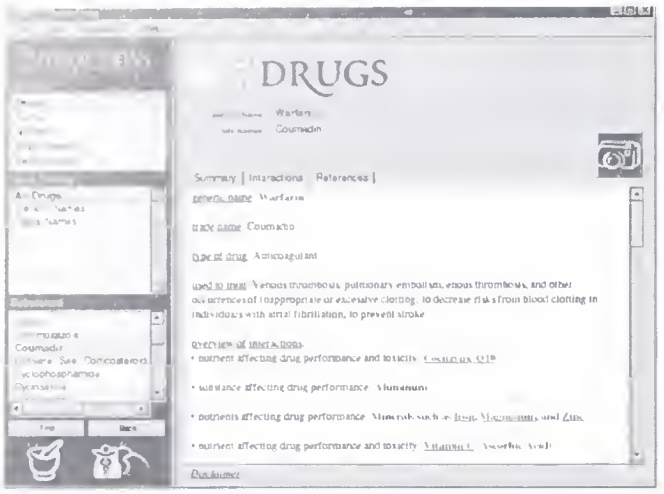


Figure 1. *Summary Screen. Summary screen showing drug, herb, or nutrient search menus on the left and an overview of warfarin (Coumadin) on the right. The "Interactions" tab in the right window can be used to provide details to the interactions summarized on this screen and the "References" tab can be used to obtain complete references and in many cases abstracts of key papers. Clicking on the red icon of a camera will bring up a diagram of the chemical structure of warfarin.*

Within this information window, there are three tabs that can be selected to choose among different types of information. The first tab is a "summary" tab that provides a quick overview of the possible interactions with herbs, drugs, food, or nutrients. The second tab is labeled "interactions" and brings up very detailed information about the mechanism of interaction, impact of herbs and supplements on drug metabolism, and plants and natural substances that may have synergistic or antagonistic properties, as well as important food-drug interaction information. Case reports are clearly labeled with "report" and other information (such as laboratory studies or clinical trials) is labeled with "research" so that the user can quickly differentiate these types of information. The third tab is a "reference" tab that provides a complete listing of all of the references used to compile the interaction monograph for a specific agent. For many references, an abstract is also provided.

Returning to the coumadin example, a wide range of potential coumadin-diet and coumadin-herb interactions were reported. The information outlined the effects of a variety of nutrients on drug performance and toxicity. Important dietary information, such as a list of foods or plants high in vitamin K or coumadins and those affecting platelet function, were also provided. Reviews of herb-coumadin interactions were discussed, as was the potential interaction with grapefruit juice. In many cases, the user could click on highlighted terms for more information or further interactions. The information is an accurate interpretation of the scientific literature available to date.

The printing feature can be used to print either a summary of the interactions, a detailed report of the interactions, or a complete report of the interactions with references. Most of the features do not require an explanation but a help menu is available that explains the layout and use of the windows/menus such as printing, searching, and referencing. Integrative Medical Arts hopes to keep a database of interactions and adverse events and has a printable report sheet for reporting cases that can be mailed, faxed, or kept in the patient's personal record.

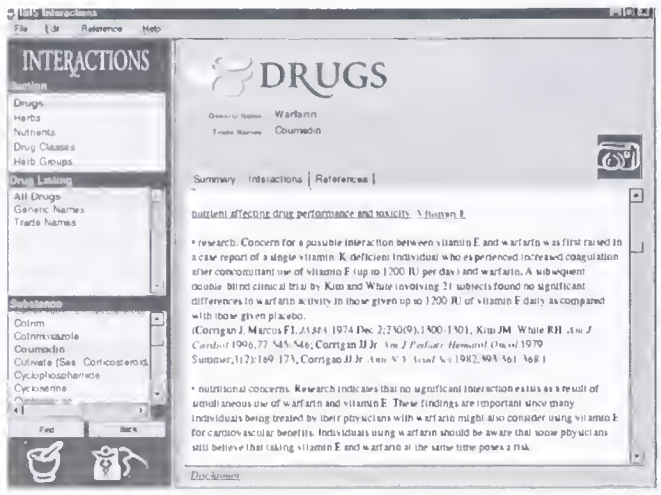


Figure 2. *Interactions Screen. Detailed information about the herb-drug or nutrient-drug information is provided in this screen. References for the information provided here can be found by clicking on the "References" tab.*

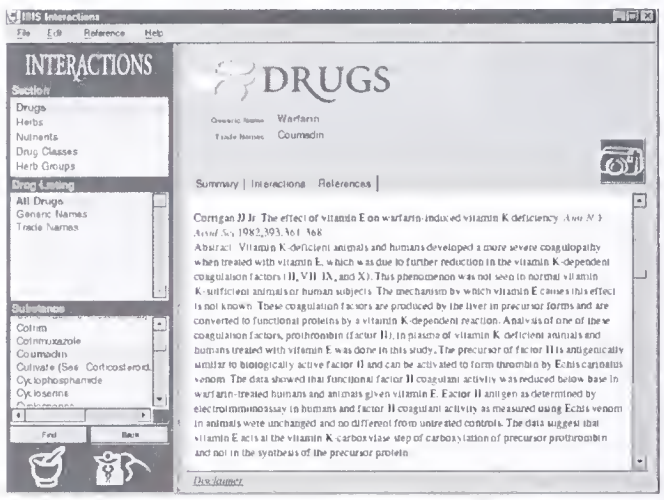


Figure 3. *References Screen. A major strength of this software is its thorough referencing of all drug-herb or drug-nutrient interactions summarized. Abstracts are provided for any of the major papers used in the preparation of the IBIS-Interactions Database.*

The team of creators and reviewers for the CD include naturopaths, pharmacists, medical doctors, practitioners of Traditional Chinese Medicine, and other allied health workers and researchers. The referencing is quite detailed and thorough and the information in the database is scientific. The nutrients listing is fairly exhaustive and includes even the latest supplements in the health food craze. Integrative Medical Arts hopes to keep a database of interactions and adverse events and has a printable report sheet for reporting cases that can be mailed, faxed, or kept in the patient's personal record. For health care practitioners looking for a quick reference, IBIS Interactions™ is an excellent resource. It is simple to use, offers a great deal of information for safely combining medications and supplements, and is extremely well referenced. There are, however, some deficiencies in this program. While there is a great deal of general information on herbal therapies in the herb class/pharmacodynamics section, only 22 herbs are specifically named in the herb section. In addition, there is a significant delay in displaying interaction data. Despite these drawbacks, it is still a quick and easy way to find information that is not readily available in standard medical texts. While the $99.95US cost may seem prohibitive, IBIS Interactions™ is a worthwhile investment for pharmacists or primary care physicians hoping to save time when dealing with questions of supplement safety and compatibility.

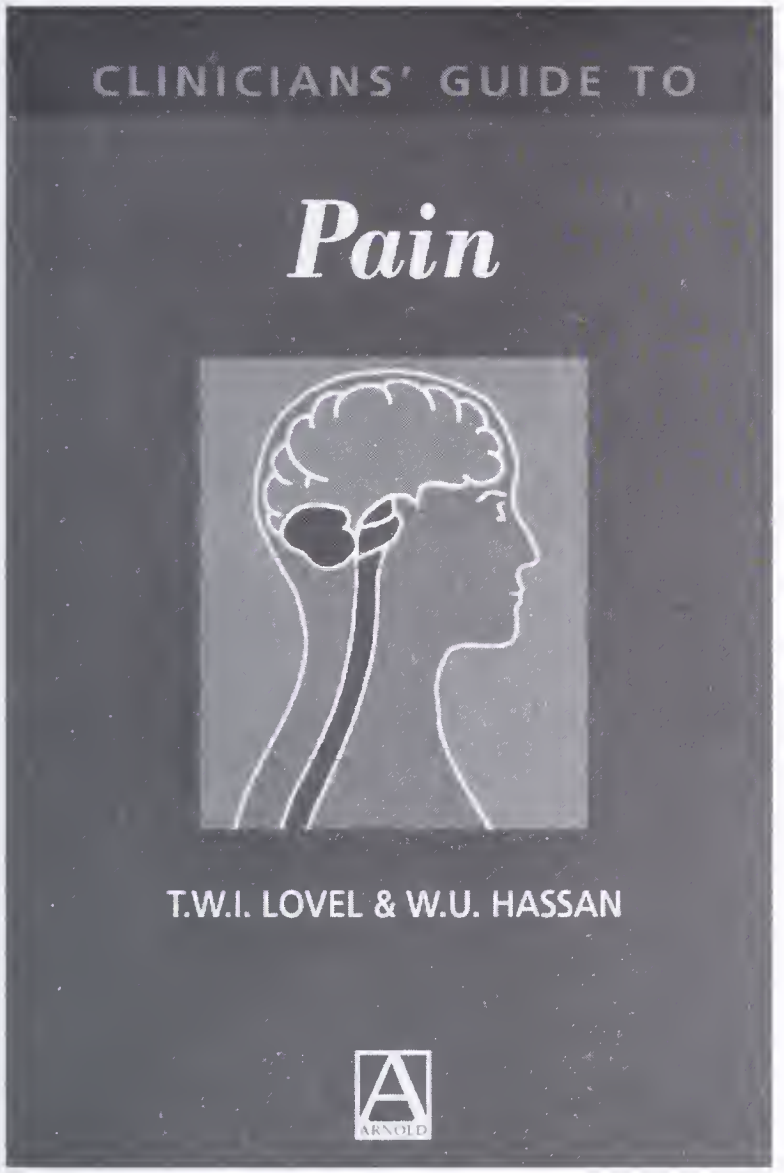
UTMJ Reviews – Family Medicine

Clinicians' Guide to Pain

Reviewed by Elizabeth Gold, B.Sc. (0T2)

Written by: T.W.I. Lovel and W.U. Hassan
Publisher: Arnold
Date of Publication: 1999
Number of Pages: 191
Cost: Paperback edition, $79.95 (CDN)

Strengths:	Practical, well written, can be read in its entirety or in sections
Weaknesses:	Too concise, little discussion of non-pharmacological treatments
Target audience:	Family physicians and residents, allied health professionals



Pain is one of the most common reasons that people seek medical attention and it is the most common symptom of patients with cancer and rheumatic diseases. However, many patients are not comfortable discussing pain with their physician, despite the significant physical, emotional, psychological and spiritual distress pain may cause them. Likewise, many physicians are not adequately trained in pain management. Although the causes of pain are generally not well understood, there have been huge improvements in the treatments of certain types of pain. *Clinicians' Guide to Pain* is divided into two parts, the first on cancer pain and the second on rheumatic diseases and musculoskeletal disorders. The authors, Lovel and Hassan, are specialists in palliative medicine and in rheumatology, respectively.

The first chapter in Part One discusses patients' fears and perceptions of cancer pain. It also presents a review of some recently published studies that outline the difficulties in accurately and objectively measuring pain and treatment outcomes. This chapter raises a variety of important issues and questions. However, the information could have been summarized in a more in-depth manner at the end of the chapter. The mechanisms of cancer pain are dealt with in a very brief two-page summary in chapter two. This chapter would have benefited from one or two simple figures to illustrate the text. The rest of Part One deals primarily with cancer pain management. Chapter three presents an overview of the opioid analgesic drugs and their uses in the treatment of cancer pain, while cor-

[illegible] are succinctly reviewed in chapter nine. The other [illegible] at specific types of cancer pain such as bone pain [illegible] steps for treatment.

The first chapter in Part Two contains a good overview of the pathophysiology and pharmacological treatment of joint pain and makes excellent use of figures. Subsequent chapters summarize rheumatic diseases including rheumatoid arthritis, osteoarthritis, low back pain and osteoporosis. Each chapter is organized into sections on clinical features and management. The final chapter is an illustrated guide to intra- and para-articular corticosteroid injections.

The overall strengths of *Clinicians' Guide to Pain* are in its layout and organization. Tables, figures, page headings, and reference lists at the end of each chapter make the book easy to use. Case reports are presented in boxes throughout the text as examples to illustrate important points. Any weaknesses are primarily due to the book's extreme brevity. Readers wanting more information on pain mechanisms, chronic pain, intractable pain and non-pharmacological treatments will have to seek other resources, the best of which is the latest edition of *Textbook of Pain*.[1] This massive but superb text discusses the basic aspects, clinical states and therapeutics of pain in extraordinary detail and is a very useful reference text, particularly for the specialist.

One of the advantages to this paperback edition of a *Clinicians' Guide to Pain* is that you will not get carpal tunnel syndrome from reading it or low back pain from carrying it. It is unfortunate, therefore, that the small size does not correlate with an even smaller price. Basic pain management is required knowledge for all physicians. While this short guide focuses primarily on the management of cancer and rheumatic pain, the sections on the pharmacological treatment of pain and the mechanisms of action of commonly prescribed drugs such as NSAIDs would be useful for any family physician. I also recommend it for time–pressed medical students.

References

1. Wall PD and Melzack R. (1999). *Textbook of Pain, 4th ed.* Churchill Livingstone: New York. $424.00 (CDN).

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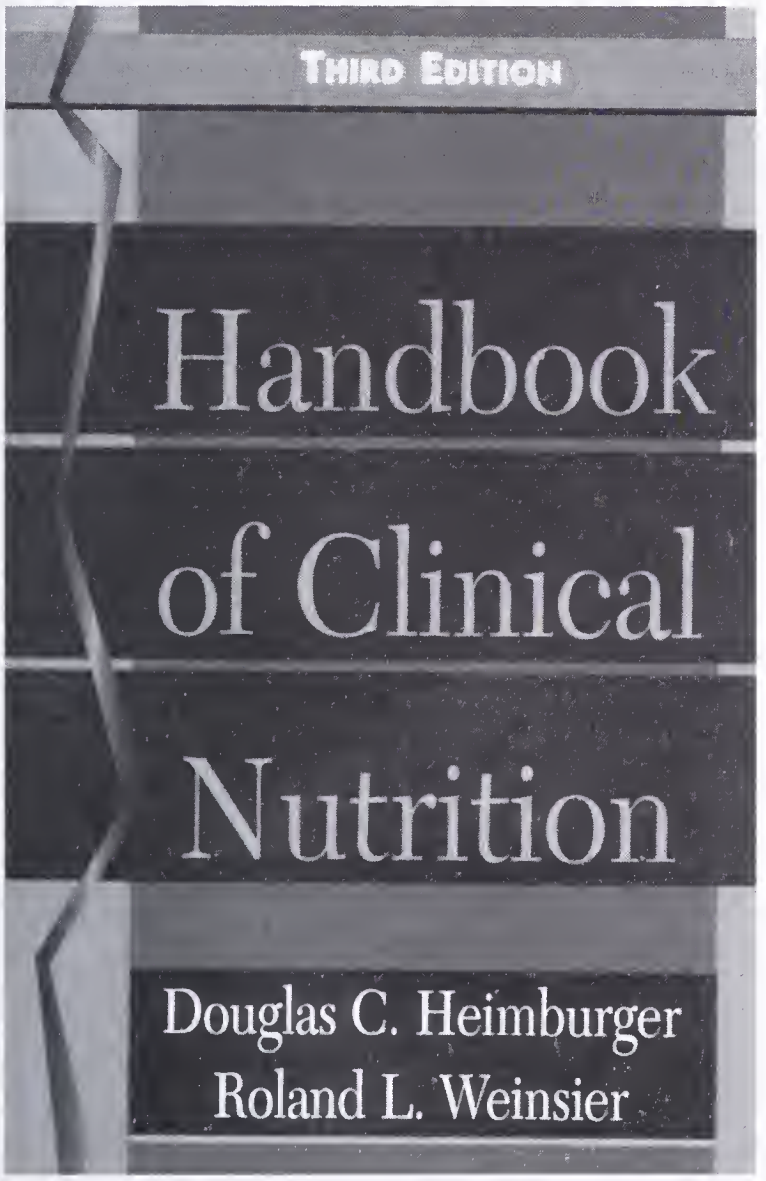
UTMJ Reviews – Family Medicine

Handbook of Clinical Nutrition, 3rd ed.

Reviewed by Andrew Brack, M.A. (0T2)

Written by: Douglas C. Heimberger and Roland L. Weinsier
Publisher: Mosby Inc.
Date of Publication: 1997
Number of Pages: 600
Cost: Paperback edition, $60.95 (CDN)

Strengths:	Concise, portable, clinically oriented
Weaknesses:	Weaknesses: will not allow physicians to answer the questions of patients interested in promoting their own health through nutrition
Target audience:	Residents and practising physicians in both hospitals and clinics



The Handbook of Clinical Nutrition grew out of a 1977 effort at the University of Alabama to give medical students, residents and ward dieticians nutritional guidance in assessing, advising and managing hospital patients. This third edition includes advances of the early '90s in the nutritional sciences, and offers greater coverage of health promotion and preventative nutrition in an era of increasing popular interest in food and health.

The *Handbook* is spiral-bound and pocket-sized for portability and easy reference. Straightforward writing, complete and succinct tables, and uncluttered line-figures present readily accessible information that is well indexed. Familiarity with basic medical terminology must inevitably be assumed, because the book covers a variety of clinical situations in a short space. It contains sections on nutrition in health maintenance, nutritional support in patient management, and nutrition in specific clinical situations.

By its very title, the section on health maintenance betrays a bias towards predominantly reactive, as opposed to proactive, nutrition. This handbook will not supply a doctor with the research surveys needed to help a patient evaluate books such as *The Zone*[1] or *Dr. Dean Ornish's Program for Reversing Heart Disease*,[2] which differ markedly from conventional dietary guidelines. There are concise tables of vitamin deficiency and toxicity symptoms, but no mention of phytoprotectants such as flavonoids or plant steroids that figure in contemporary

comes to manuals such as *Human Nutrition and Dietetics*.[3] Exposure to fluoride or aspartame, considered in the *Nutrition Recommendations* of Health Canada is also not discussed. And [illegible] of space, the *Handbook* does not include material on cultural diversity in diet such as can be found in *Nutritional Epidemiology*.[5] However, the *Handbook* does display an admirable awareness of the social and domestic context of its recommendations. The discussion of geriatric nutrition repeatedly draws the reader's attention to the many seemingly unrelated factors, for example, living alone, poor-fitting dentures and changes in taste and smell sensation that can affect diet in the elderly. The discussion of pregnancy not only outlines increased nutrient requirements but also gives specific recommendations for the nausea and vomiting, heartburn and constipation often experienced by pregnant women, thereby lessening the chance that a patient might seek relief through such risky behaviour as dietary restriction or pica.

The section on nutritional support in patient management is perhaps the forte of this handbook, as it stems directly from of the practical needs of hospital physicians that prompted the first edition. The up-to-date chapter on nutrition support teams lays out with admirable clarity typical responsibilities of various health professions. The practical grounding of this book in a U.S. health insurance environment extends even to a (brief) list of nutritional comorbidity ICD-9 codes for billing purposes. Numerous other tables summarize nutritional assessment, therapeutic diets, enteral feeding formulae, the management of diarrhoea, and drug-nutrient interactions. This handbook provides a practical and up-to-date overview of information covered in considerable depth in manuals such as *Principles of Nutritional Assessment*.[6]

The section grouped by specific clinical situations allows compact treatment of what took more voluminous form in *Nutrition and Diagnosis-Related Care*.[7] Oddly enough, much of the *Handbook's* preventative health information is given in the chapters addressing obesity, diabetes, hypertension, cardiovascular disease and cancer, an incidental consequence of a "disease-oriented approach" that allows rapid location of needed information.

The *Handbook* does not entirely fulfil the need for an up-to-date synthesis of health food initiatives, nor does it replace a textbook of nutrition. It does, however, indicate the interventions a doctor should make for the most positive effects and reliable outcomes in keeping with the current standard of care. If pricey at $60.95 (CDN), it may serve as the single book that allows discharge of a physician's nutritional responsibilities.

References

1. Sears B. (1995). *The Zone*. Harper Collins: New York.
2. Ornish D. (1990). *Dr. Dean Ornish's Program for Reversing Heart Disease*. Ivy Books: New York.
3. Garrow JS, James WPT, and Ralph A. (2000). *Human Nutrition and Dietetics, 10th ed.* Churchill Livingstone: Edinburgh. $117.00 (CDN).
4. Health Canada. (1990). *Nutrition Recommendations: The Report of the Scientific Review Committee*. $19.95 (CDN).
5. Willett W. (1988). *Nutritional Epidemiology, 2nd ed.* Oxford UP: Oxford.
6. Gibson RS. (1990). *Principles of Nutritional Assessment*. Oxford UP: New York. $102.50 (CDN).
7. Escott-Stump S. (1998). *Nutrition and Diagnosis-Related Care, 4th ed.* Williams & Wilkins: Baltimore. $77.50 (CDN).

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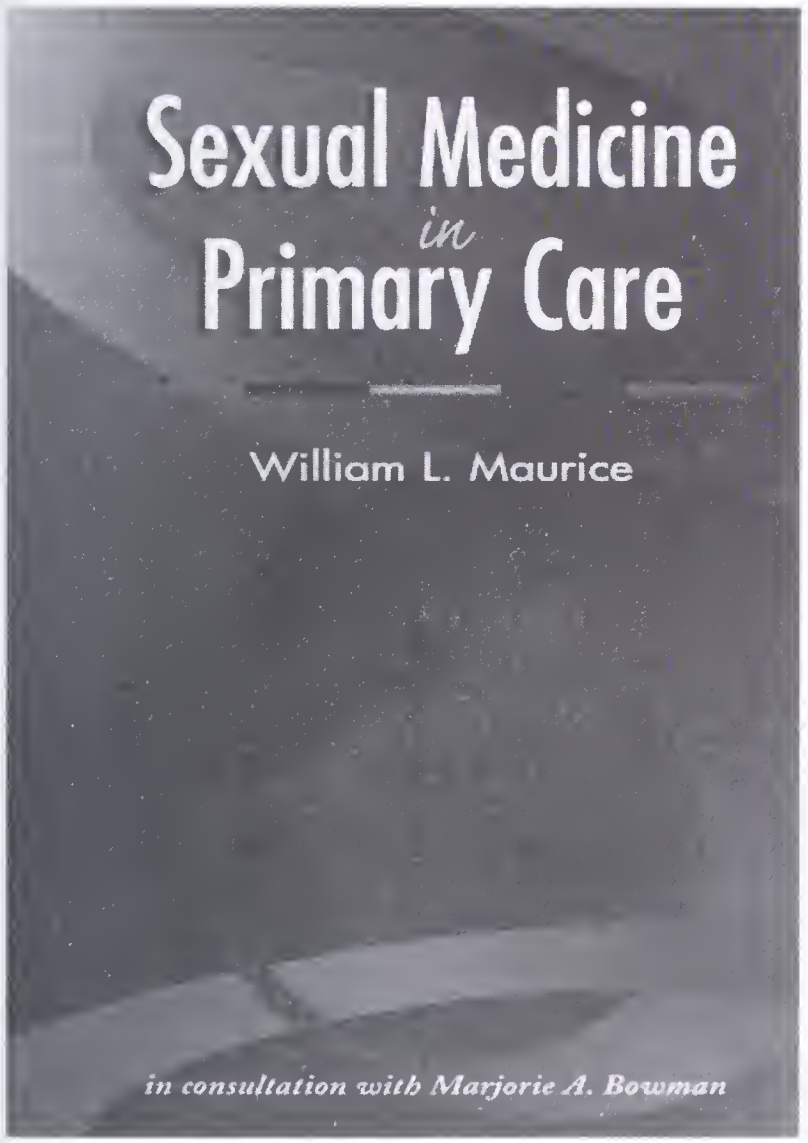
UTMJ Reviews – Family Medicine

Sexual Medicine in Primary Care

Reviewed by Helen Dempster, B.Sc.Eng., M.Sc. (0T2)

Written by: William L. Maurice
Publisher: Mosby
Date of Publication: 1999
Number of pages: 366
Cost: Paperback edition, $63.95 (CDN)

Strengths:	Interesting and easy to understand
Weaknesses:	Discussion of sexual dysfunctions too general and superficial in parts
Audience:	Undergraduate medical students, residents and practitioners of family medicine



There is growing recognition that sexuality plays a significant role in quality of life. Sexual problems may cause significant emotional and physical distress. Patients expect their family physicians to be experts in sexual health and turn to them for sound, thoughtful advice and effective intervention. Sexual inquiry and education are therefore essential components of responsible and comprehensive healthcare. Most generalists, however, feel unprepared to deal with sexual concerns. A lack of medical understanding about sexual matters combined with concerns about offending or embarrassing patients have made many physicians wary of sexual inquiry. There is also a lack of material providing practical advice in this area for primary care practitioners. Most of the currently available texts address sexual issues from the perspective of secondary care providers in gynaecology and urology, and provide only the essentials of diagnosis and management. For these reasons, *Sexual Medicine in Primary Care* is a timely and practical addition to the library of any primary care provider.

Part I of the book discusses history taking, interviewing and assessment. It provides practical advice for talking about sexual issues while preserving the dignity of the patient. In particular, sensitive areas such as sexual orientation, sexual difficulties and sexual issues in the context of medical and psychiatric disorders are discussed. Simple

questionnaires and sample interviews help the reader follow the path to a positive answer to a sexual screening question. Clinical vignettes are often used as a basis for discussion, and these are both interesting and informative. Finally, the Appendices contain complete samples of first-assessment interviews and case histories that are helpful learning tools for students, residents and clinicians.

Part II of the book focuses on the diagnosis and treatment of the most common sexual dysfunctions, such as low desire, erectile disorders and intercourse difficulties in women. Medical definitions and classifications are presented in a readable and organized format. The investigative process, from the history and physical to laboratory studies, is simply and methodically reviewed, and the rationale for each question or procedure is explained. The author outlines when treatment is within the realm of the family physician and describes situations in which referral to another health care provider may be necessary. The Appendices provide an extensive table of medications that interfere with sexual function and lists of useful resources, including web sites and selected self-help books, for both patients and health professionals.

There are two very strong points about this book. First, it provides information that is practical and relevant. Second, it delivers this information in a very readable and understandable format. The most important points of a given paragraph or section are highlighted with boldfaced sentences in the margin. Boxes emphasize important facts, flow charts and lists. Clinical vignettes and sample interviews add a personal touch to the medical facts. The summaries at the end of each chapter do an excellent job of reiterating only the most important points.

The main caveat I would give to anyone reading *Sexual Medicine in Primary Care* is that the book is limited to an approach towards common sexual problems. It is not a reference text on the pathobiology of sexual disorders and many dysfunctions are discussed only superficially. For some of the conditions with a definite organic etiology, I found this to be a weakness. Figures highlighting the relevant anatomy and reviews of both the normal and abnormal physiology would have been an asset.

Nonetheless, *Sexual Medicine in Primary Care* does provide a practical and relevant review of an area of medicine that many health professionals are reluctant to discuss with their patients. I would recommend it to medical students particularly for its advice on sexual inquiry, as this is a responsibility of clerks and residents in any discipline. As a review of common sexual dysfunctions, this book would also be a useful resource for any family physician.

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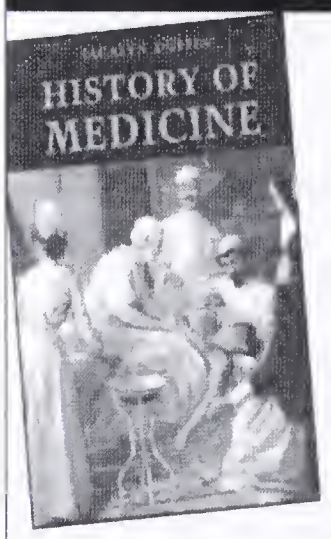

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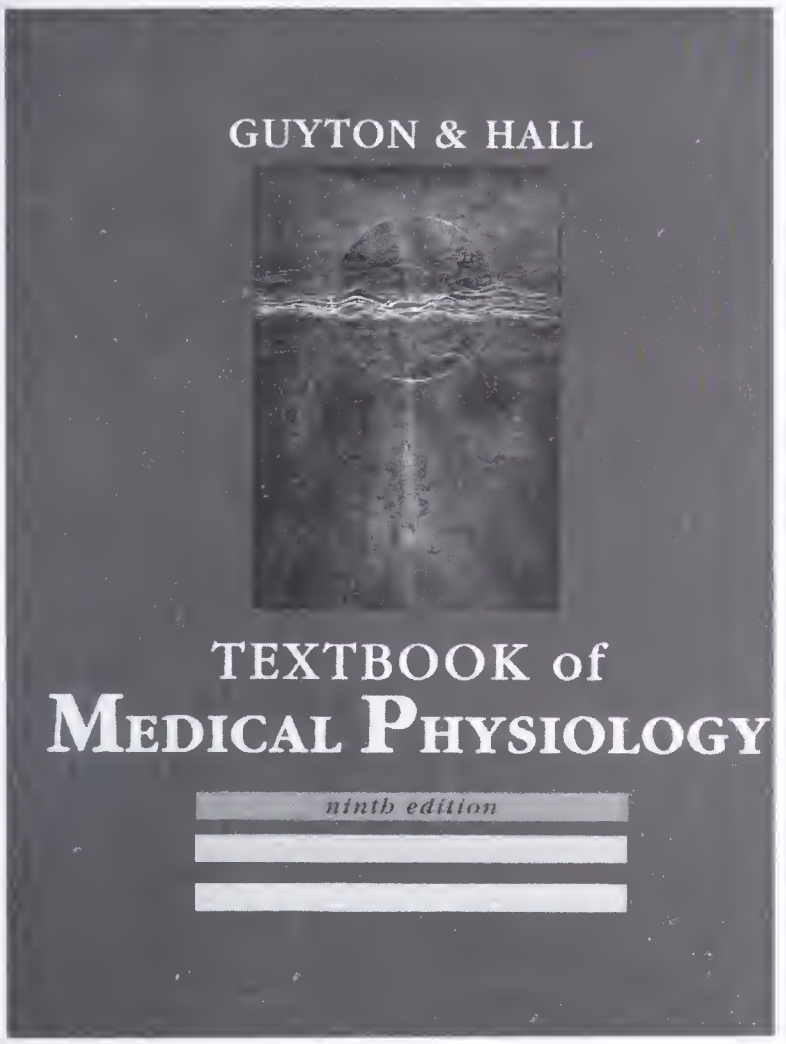
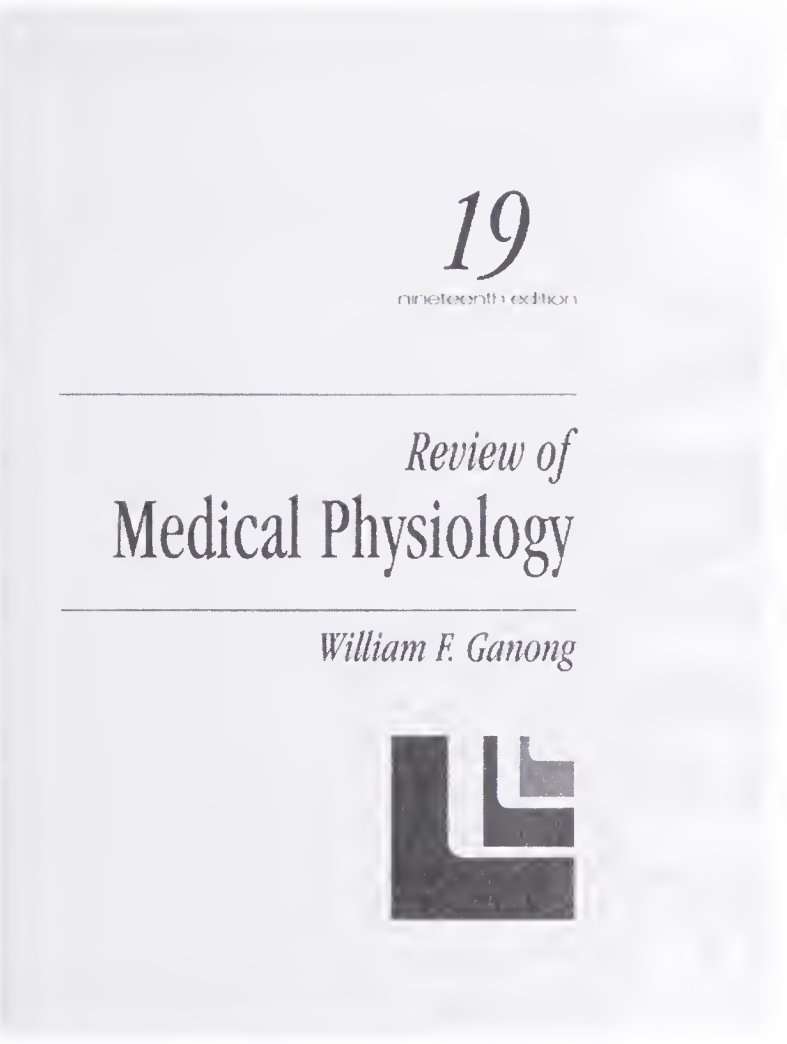
UTMJ Reviews – The Essentials

Reviewed by Sharon Cushing, B.Sc. (0T3) and Angela Marrocco, B.Sc., BPHE (0T3)

Textbook of Medical Physiology, 9th ed.
Written by: Arthur C. Guyton and John E. Hall
Publisher: W.B. Saunders Company
Date of Publication: 1996
Number of pages: 1148
Cost: Hardcover edition, $101.00 (CDN)

Review of Medical Physiology, 19th ed.
Written by: William F. Ganong
Publisher: Appleton & Lange
Date of Publication: 1999
Number of pages: 851
Cost: Paperback edition, $60.40 (CDN)





Physiology provides a foundation for the understanding of all medical disciplines. There is a vast array of medical physiology texts available to students. Guyton and Hall's *Textbook of Medical Physiology* and Ganong's Review of *Medical Physiology* are both great choices for first year students. In choosing a text, however, one needs to define a price range and a style that he or she will find helpful not only for initial learning, but also for future reference.

Guyton and Hall's *Textbook of Medical Physiology* has often been regarded as the hallmark for medical students. It is an in-depth and comprehensive guide to physiology. Each of the major topics in physiology is explored in ample detail and is accompanied by a discussion of pathology and clinical points of interest. For example, the section on "The Kidneys and Body Fluids" is supplemented by a chapter covering diuretics and kidney diseases. The concepts defined throughout the text are accompanied by numerous illustrations that facilitate the reader's understanding. The Table of Contents is well organized and allows for easy reference.

The authors have also realized that an understanding of physiology is often helped by an understanding of other topics. Thus, they have included anatomical, biochemical and special interest information in smaller fonts so that it is easy to identify and separate them from the fundamental physiological information presented in larger fonts. Guyton and Hall have included an interesting chapter on "Aviation, Space and Deep Sea Diving Physiology," as well as a chapter on "Sports Physiology" that one might not find in other physiology texts. In general, the greatest strength of this text is its broad and expansive presentation of physiology, making it an important reference that will serve students well throughout their medical education and in the years beyond.

Although Guyton and Hall's *Textbook of Medical Physiology* provides a complete and thorough resource for medical students, the volume of information presented may be overwhelming. In particular, the discussion on Electrocadiographic Interpretation of Cardiac Muscle Abnormalities is difficult to follow and contains extraneous information that does not facilitate the reader's understanding. In addition, the small fonts and trichromatic diagrams tend to make this text difficult to read. For those with little background in physiology, a more basic textbook may be advised while others may prefer a more abridged textbook of physiology, such as *Review of Medical Physiology*. Students may also wish to wait until the tenth edition, expected in August 2000, is released.

Ganong's Review of *Medical Physiology* is a concise, yet comprehensive, reference for medical students. Although it is a physiology text, the author also touches on many of the biochemical details of the body.

Ganong's writing style is very clear and easy to read, particularly for students with some background in physiology. *Review of Medical Physiology* has excellent cross-referencing within the text, so that students can review words or concepts with which they are not familiar. This book also includes an excellent introductory chapter covering the basic concepts of physiology. Students with little scientific background may be slightly frustrated by the lack of a glossary. For definitions of simple or non-physiological terms, one needs to look elsewhere. Readers who need detailed explanations or dislike jumping back and forth between pages may not like Ganong's style. Each section is concise and does not include anything that is not essential to the main point. For extra detail, one must utilize the cross-references and seek out the appropriate chapter.

Review of Medical Physiology is organized according to the major body systems. Each chapter has a brief introduction and is then filled with sub-headings and bold print for easy reference. The text also has a comprehensive Table of Contents and Index. As well as having chapters that are easy to read from start to finish, Ganong's text is a great place to look up a single term or concept. The diagrams and tables are neither flashy nor overly complicated. They are plentiful and, in keeping with the style of the text, they are simple and clear.

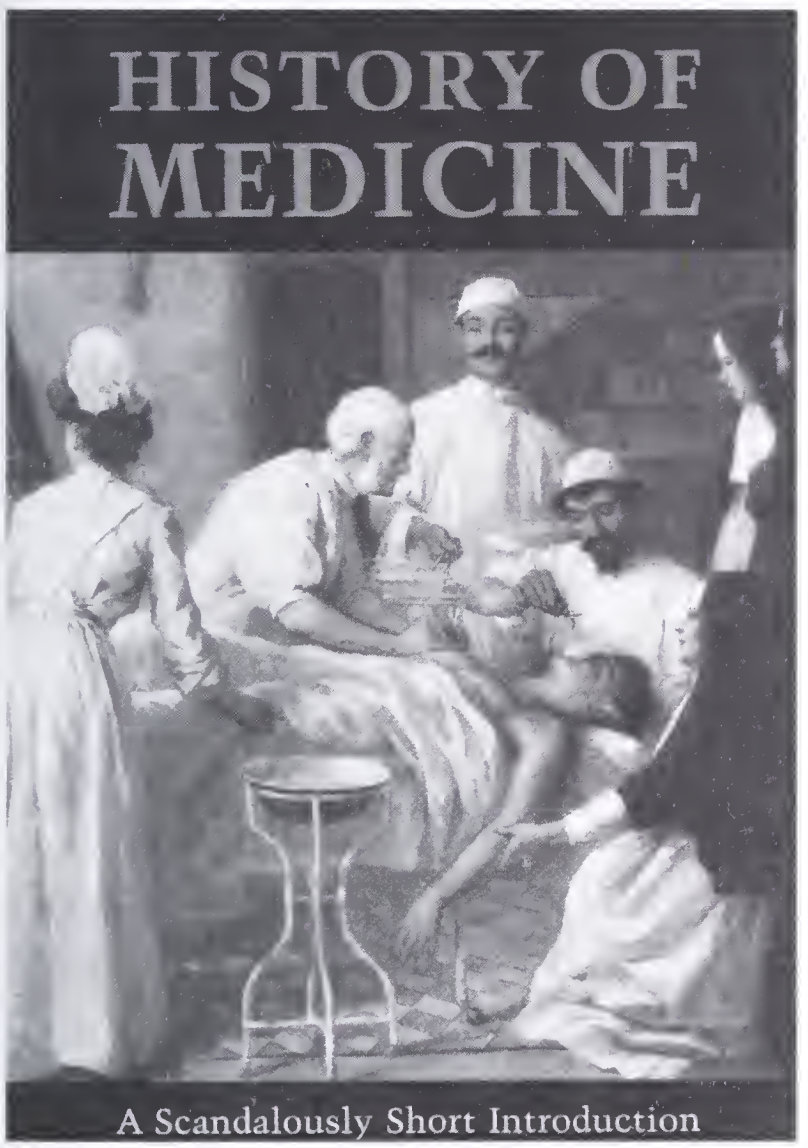
This text is a fantastic reference. Those with no physiology background would be wise to read some passages before purchasing it to ensure that it does not use too much jargon. It is effective for learning new concepts and for reviewing those already understood. This book is highly recommended as a first year medical textbook and a reference for future years.

UTMJ Reviews – History of Medicine

History of Medicine: A Scandalously Short Introduction

Reviewed by Sacha Agrawal, B.Sc. (OT2) and Inbal Gafni, B.Sc., M.Sc.

Written by: Jacalyn Duffin
Publisher: University of Toronto Press
Date of Publication: 1999
Number of pages: 432
Cost: Cloth edition, $65.00; paperback edition, $24.95



Hippocrates is often revered as the "father of medicine". He emphasized case histories, natural causes of disease, and a strict ethical code, concepts that are still with us today some 2500 years later. We might criticise him, however, for promoting the theory that illness is the result of an imbalance of bodily fluids he referred to as "humours," for teaching medicine only to men, and for forbidding abortion. Is Hippocrates, then, a hero or a villain?

For years, Dr. Jacalyn Duffin's first-year medical students have answered "hero!" without fail. This answer is instructive, she tells us, because it demonstrates how eager they are to assume a glorious past for what, from their perspective, is a glorious profession. But Duffin objects, both to the answer and to the underlying attitude. She asserts that because history is a complex enterprise of selecting and interpreting evidence, neat labels like "hero" or "villain" cannot easily be applied. She challenges her students' unquestioning acceptance of their profession. Her book is meant as an introduction for students, scientists and practitioners who want to develop tools for thinking critically about the history of medicine.

Duffin offers are decidedly post-modern. She encourages the reader to think of theories of illness as social constructs, influenced by prevailing attitudes and beliefs, both scientific and non-scientific. She cites as an example homosexuality, which was viewed first as sinful and therefore criminal in the middle ages, then as a disease by the late 19th century and well into the 20th century, and now as a variation of normal. This metamorphosis, she asserts, occurred with changes in the cultural and socio-political climate. She also discourages value judgements about the past, like "hero" and "villain." Instead, the reader is urged to ask why people believed and behaved the way they did, and what led to changes in those ideas and practices. To return to our example of Hippocrates, we might find it unsurprising that physicians would transform the reigning philosophical doctrine of four elements into a theory of four humours when conjecturing about physiology and disease. Similarly, Hippocrates' requirement that doctors swear to teach their art only to men should be examined in the context of the role that men and women played in Ancient Greece.

Duffin structures her work around discrete histories of selected medical sciences (anatomy, physiology, pathology and pharmacology) and specialities (haematology, surgery, obstetrics and gynaecology, psychiatry, paediatrics and family medicine). She also includes chapters on health care delivery, epidemic diseases, technology and, as a conclusion, a "How-to" chapter on studying medical history. This "scandalously short introduction" twists and turns through various past peoples, places and ideas. Duffin also incorporates some important ideas about history as an exercise (historiography) and about the intersection of science and philosophy with medicine. The result is a style that, although diffuse, is provocative. The chapters are written to stand independently, a format that is useful both to medical students who want to "follow along" as they proceed through their curriculum, and to those who have specific interests. The corollary is that someone who reads the book from cover to cover may want a more integrated and developed approach to the many interesting ideas she presents.

The text is punctuated with boxes containing anecdotes, quotations as well as other ideas and figures, emphasizing important points and adding interest and flavour. Because some of these inclusions are also examples of primary sources of historical information, the reader has an opportunity to do history by practising observation and interpretation, often without the benefit of the author's own analysis. Duffin's educational objectives and extensive reading lists (which include Canadian sources) enhance the book's utility as a learning tool.

As a historian, Duffin is aware that her own identity plays an important role in how she portrays her subject. She accepts and embraces her biases as a woman, haematologist and historian. For example, she includes feminist theory in her discussion of obstetrics and gynaecology, she devotes a whole chapter to explaining "why blood is special," and she incorporates a healthy dose of history theory into her analysis. Her identity also comes through in her style: her vibrant personality and gifts as a teacher shine throughout the book, distinguishing it as a fun and thoughtful introduction to the topic.

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1. Reinders FX, Chalin C, and Meier HMR. (1993). Alzheimer's disease: Understanding the patient and caregiver. *UTMJ*. 70: 16-20.
2. Kocsis JH, Davis JM, Katz MM, *et al.* (1985). Depressive behavioral and hyperactive adrenocortical function. *Am J Psychiatry*. 142: 1291-1298.

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3. Smith MHD and Teele DW. (1995). Tuberculosis. *In: Infectious Diseases of the Fetus and Newborn Infant, 4th ed.* Remington JS and JO Klein JO (eds). WB Saunders: Philadelphia, pp. 1074-1086.

4. Podolsky DK and KJ Isselbacher. (1998). Major complications of cirrhosis (ascites). *In: Harrison's Principals of Internal Medicine, 14th ed.* Fauci AS *et al.* (eds). McGraw-Hill, New York, pp. 210-214.

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NORVASC*

(amlodipine besylate)

ef Prescribing Information

Antianginal Agent

ACTION AND CLINICAL PHARMACOLOGY

A besylate is a calcium ion influx inhibitor (calcium entry blocker or calcium ion antagonist) of the dihydropyridine class of calcium antagonists

INDICATIONS AND CLINICAL USE

Hypertension

besylate is indicated in the treatment of mild-to-moderate essential hypertension.

A may be used in those patients in whom treatment with diuretics or beta-blockers was found been associated with unacceptable adverse effects. NORVASC can be tried as an initial agent in patients in whom the use of diuretics and/or beta-blockers is contraindicated or in patients with medical which these drugs frequently cause serious adverse effects. Combination of NORVASC with a beta blocking agent or an angiotensin converting enzyme inhibitor has been found to be compatible and additive antihypertensive effect

Chronic Stable Angina

NORVASC is indicated for the management of chronic stable angina (effort-associated angina) in patients who symptomatic despite adequate doses of beta-blockers and/or organic nitrates or who cannot tolerate those agents. NORVASC may be tried in combination with beta-blockers in chronic stable angina in patients with normal ventricular function. When such concomitant therapy is introduced, care must be taken to monitor blood pressure closely since hypotension can occur from the combined effects of the drugs

CONTRAINDICATIONS

NORVASC (amlodipine besylate) is contraindicated in patients with hypersensitivity to the drug or other dihydropyridines and in patients with severe hypotension (less than 90 mmHg systolic)

WARNINGS

Increased Angina and/or Myocardial Infarction

Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration and/or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been elucidated

Outflow Obstruction (Aortic Stenosis)

NORVASC should be used with caution in a presence of fixed left ventricular outflow obstruction (aortic stenosis)

Use in Patients with Impaired Hepatic Function

There are no adequate studies in patients with liver dysfunction and dosage recommendations have not been established. In a small number of patients with mild-to-moderate hepatic impairment given single dose of 5 mg, amlodipine half-life has been prolonged. NORVASC should, therefore, be administered with caution in these patients and careful monitoring should be performed. A lower starting dose may be required (see **DOSAGE AND ADMINISTRATION**).

Beta-blocker Withdrawal

NORVASC gives no protection against the dangers of abrupt beta-blocker withdrawal and such withdrawal should be done by the gradual reduction of the dose of beta-blocker

PRECAUTIONS

Use in Patients with Congestive Heart Failure

Although generally calcium channel blockers should only be used with caution in patients with heart failure, it has been observed that NORVASC had no overall deleterious effect on survival and cardiovascular morbidity in both short-term and long-term clinical trials in these patients. While a significant proportion of the patients in these studies had a history of ischemic heart disease, angina or hypertension, the studies were not designed to evaluate the treatment of angina or hypertension in patients with concomitant heart failure

Hypotension

NORVASC (amlodipine besylate) may occasionally precipitate symptomatic hypotension. Careful monitoring of blood pressure is recommended, especially in patients with a history of cerebrovascular insufficiency, and those taking medications known to lower blood pressure

Peripheral Edema

Mild-to-moderate peripheral edema was the most common adverse event in the clinical trials (see **ADVERSE REACTIONS**). The incidence of peripheral edema was dose-dependent and ranged in frequency from 3.0 to 10.8% in 5 to 10 mg dose range. Care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction

Use in Pregnancy

Although amlodipine was not teratogenic in the rat and rabbit some dihydropyridine compounds have been found to be teratogenic in animals. In rats, amlodipine has been shown to prolong both the gestation period and the duration of labor. There is no clinical experience with NORVASC in pregnant women. NORVASC should be used during pregnancy only if the potential benefit outweighs the potential risk to the mother and fetus.

Nursing Mothers

It is not known whether amlodipine is excreted in human milk. Since amlodipine safety in newborns has not been established, NORVASC should not be given to nursing mothers

Use in Children

The use of NORVASC is not recommended in children since safety and efficacy have not been established in that population.

Use in Elderly

In elderly patients (>65 years) clearance of amlodipine is decreased with a resulting increase in AUC. In clinical trials the incidence of adverse reactions in elderly patients was approximately 6% higher than that of younger population (<65 years). Adverse reactions include edema, muscle cramps and dizziness. NORVASC should be used cautiously in elderly patients. Dosage adjustment is advisable (see **DOSAGE AND ADMINISTRATION**).

Interaction with Grapefruit Juice

Published data indicate that through inhibition of the cytochrome P450 system, grapefruit juice can increase plasma levels and augment pharmacodynamic effects of some dihydropyridine calcium channel blockers. Following oral administration of 10 mg amlodipine to 20 male volunteers, pharmacokinetics of amlodipine were similar when amlodipine was administered with and without grapefruit juice

Drug Interactions

As with all drugs, care should be exercised when treating patients with multiple medications. Dihydropyridine calcium channel blockers undergo biotransformation by the cytochrome P450 system, mainly via CYP 3A4 isoenzyme. Coadministration of amlodipine with other drugs which follow the same route of biotransformation may result in altered bioavailability of amlodipine or these drugs. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio, and especially in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered amlodipine to maintain optimum therapeutic blood levels

Drugs known to be inhibitors of the cytochrome P450 system include: azole antifungals, cimetidine, cyclosporine, erythromycin, quinidine, terfenadine, warfarin

Drugs known to be inducers of the cytochrome P450 system include: phenobarbital, phenytoin, rifampin.

Drugs known to be biotransformed via P450 include: benzodiazepines, flecainide, imipramine, propafenone, theophylline

Amlodipine has a low (rate of first-pass) hepatic clearance and consequent high bioavailability, and thus, may be expected to have a low potential for clinically relevant effects associated with elevation of amlodipine plasma levels when used concomitantly with drugs that compete for or inhibit the cytochrome P450 system.

Cimetidine, Warfarin, Cyclosporin, Digoxin: Pharmacokinetic interaction studies with amlodipine in healthy volunteers have indicated

- **cimetidine** did not alter the pharmacokinetics of amlodipine
- amlodipine did not change **warfarin**-induced prothrombin response time
- amlodipine does not significantly alter the pharmacokinetics of **cyclosporin**.
- amlodipine did not change serum **digoxin** levels or **digoxin** renal clearance

Antacids

Concomitant administration of Maalox® (magnesium hydroxide and aluminum hydroxide) had no effect on the dis- of a single 5 mg dose of amlodipine in 24 subjects

Beta-blockers: When beta-adrenergic receptor blocking drugs are administered concomitantly with NORVASC, should be carefully monitored since blood pressure lowering effect of beta-blockers may be augmented by additive effect on peripheral vascular resistance

ADVERSE REACTIONS

NORVASC (amlodipine besylate) has been administered to 1,714 patients (805 hypertensive and 909 angina patients) in controlled clinical trials (vs placebo alone and with active comparative agents). Most adverse reactions reported during therapy were of mild-to-moderate severity

Hypertension

In the 805 hypertensive patients treated with NORVASC in controlled clinical trials, adverse effects were reported in 29.9% of patients and required discontinuation of therapy due to side effects in 1.9% of patients. The most common adverse reactions in controlled clinical trials were: edema (8.9%), and headache (8.3%). The following adverse reactions were reported with an incidence of >0.5% in the controlled clinical trials program (n=805)

Cardiovascular: edema (8.9%), palpitations (2.0%), tachycardia (0.7%), postural dizziness (0.5%). **Skin and Appendages:** pruritus (0.7%). **Musculoskeletal:** muscle cramps (0.5%). **Central and Peripheral Nervous System:** headache (8.3%), dizziness (3.0%), paresthesia (0.5%). **Autonomic Nervous System:** flushing (3.1%), increased sweating (0.9%), dry mouth (0.7%). **Psychiatric:** somnolence (1.4%). **Gastrointestinal:** nausea (2.4%), abdominal pain (1.1%), dyspepsia (0.6%), constipation (0.5%). **General:** fatigue (4.1%), pain (0.5%).

Angina

In the controlled clinical trials in 909 angina patients treated with NORVASC, adverse effects were reported in 30.5% of patients and required discontinuation of therapy due to side effects in 0.6% of patients. The most common adverse reactions reported in controlled clinical trials were: edema (9.9%) and headache (7.8%).

The following adverse reactions occurred at an incidence of ≥0.5% in the controlled clinical trials program (n=909)

Cardiovascular: edema (9.9%), palpitations (2.0%), postural dizziness (0.6%). **Skin and Appendages:** rash (1.0%), pruritus (0.8%). **Musculoskeletal:** muscle cramps (1.0%). **Central and Peripheral Nervous System:** headache (7.8%), dizziness (4.5%), paresthesia (1.0%), hypoesthesia (0.9%). **Autonomic Nervous System:** flushing (1.9%). **Psychiatric:** somnolence (1.2%), insomnia (0.9%), nervousness (0.7%). **Gastrointestinal:** nausea (4.2%), abdominal pain (2.2%), dyspepsia (1.4%), diarrhea (1.1%), flatulence (1.0%), constipation (0.9%). **Respiratory System:** dyspnea (1.1%). **Special Senses:** abnormal vision (1.3%), tinnitus (0.6%). **General:** fatigue (4.8%), pain (1.0%), asthenia (1.0%).

NORVASC has been evaluated for safety in about 11,000 patients with hypertension and angina.

The following events occurred in <1% but >0.1% of patients in comparative clinical trials (double-blind comparative vs placebo or active agents; n = 2,615) or under conditions of open trials or marketing experience where a causal relationship is uncertain

Cardiovascular: arrhythmia (including ventricular tachycardia and atrial fibrilation), bradycardia, hypotension, peripheral ischemia, syncope, tachycardia, postural dizziness, postural hypotension. **Central and Peripheral Nervous System:** hypoesthesia, tremor, vertigo. **Gastrointestinal:** anorexia, constipation, dysphagia, vomiting, gingival hyperplasia. **General:** asthenia†, back pain, hot flushes, malaise, rigors, weight gain. **Musculoskeletal System:** arthralgia, arthrosis, myalgia. **Psychiatric:** sexual dysfunction (male† and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization. **Respiratory System:** epistaxis. **Skin and Appendages:** pruritus†, rash erythematous, rash maculopapular, erythema multiforme. **Special Senses:** conjunctivitis, diplopia, eye pain, tinnitus. **Urinary System:** micturition frequency, micturition disorder, nocturia. **Autonomic Nervous System:** dry mouth, increased sweating. **Metabolic and Nutritional:** thirst. **Hemopoietic:** purpura

† These events occurred in less than 1% in placebo-controlled trials, but the incidence of these side effects was between 1% and 2% in all multiple dose studies.

The following events occurred in ≤0.1% of patients: cardiac failure, skin discoloration, urticaria, skin dryness, Stevens-Johnson syndrome, alopecia, twitching, ataxia, hypertonia, migraine, apathy, amnesia, gastritis, pancreatitis, increased appetite, coughing, rhinitis, parosmia, taste perversion, and xerophthalmia

Isolated cases of angioedema have been reported. Angioedema may be accompanied by breathing difficulty. In postmarketing experience, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis) in some cases severe enough to require hospitalization have been reported in association with use of amlodipine.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms

Overdosage can cause excessive peripheral vasodilation with marked and probably prolonged hypotension and possibly a reflex tachycardia. In humans, experience with overdosage of NORVASC (amlodipine besylate) is limited. When amlodipine was ingested at doses of 105-250 mg some patients remained normotensive with or without gastric lavage while another patient experienced hypotension (90/50 mmHg) which normalized following plasma expansion. A patient who took 70 mg of amlodipine with benzodiazepine developed shock which was refractory to treatment and died. In a 19 month-old child who ingested 30 mg of amlodipine (about 2 mg/kg) there was no evidence of hypotension but tachycardia (180 bpm) was observed. Ipecac was administered 3.5 hrs after ingestion and on subsequent observation (overnight) no sequelae were noted.

Treatment

Clinically significant hypotension due to overdosage requires active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output. A vasoconstrictor (such as norepinephrine) may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. As NORVASC is highly protein bound, hemodialysis is not likely to be of benefit. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade. Clearance of amlodipine is prolonged in elderly patients and in patients with impaired liver function. Since amlodipine absorption is slow, gastric lavage may be worthwhile in some cases.

DOSAGE AND ADMINISTRATION

Dosage should be individualized depending on patient's tolerance and responsiveness. For both hypertension and angina, the recommended initial dose of NORVASC (amlodipine besylate) is 5 mg once daily. If necessary, dose can be increased after 1-2 weeks to a maximum dose of 10 mg once daily

Use in the Elderly or in Patients with Impaired Renal Function

The recommended initial dose in patients over 65 years of age or patients with impaired renal function is 5 mg once daily. If required, increasing in the dose should be done gradually and with caution (see **PRECAUTIONS**).

Use in Patients with Impaired Hepatic Function

Dosage requirements have not been established in patients with impaired hepatic function. When NORVASC is used in these patients, the dosage should be carefully and gradually adjusted depending on patient's tolerance and response. A lower starting dose of 2.5 mg once daily should be considered (see **WARNINGS**).

DOSAGE FORMS

Availability

NORVASC is available as white octagonal tablets containing amlodipine besylate equivalent to 2.5, 5 and 10 mg amlodipine per tablet. The respective tablet strengths are debossed on one tablet face as "NRV 2.5", "NRV 5" and "NRV 10" with "Pfizer" on the opposite face. The 5 mg tablet is scored. Supplied in white plastic (high density polyethylene) bottles of 100 tablets for each strength. Also the 5 mg and 10 mg are supplied in bottles of 250 tablets.

STORAGE

Store at 15-30°C. Protect from light.

REFERENCES: ANGINA

1. NORVASC® Product Monograph, Pfizer Canada Inc., Dec. 19, 1997
2. Purcell H, Waller DG, Fox K. Therapeutic focus: calcium antagonists in cardiovascular disease. Br J Clin Pract 1989;43(10):369-79.
3. Salerno SM and Zugibe FT. Calcium channel antagonists: What do the second generation agents have to offer? Postgrad Med 1994;95(1):181-90.
4. Deanfield JE et al. Amlodipine reduces transient myocardial ischemia in patients with coronary artery disease: double-blind circadian anti-ischemia program in Europe (CAPE trial). J Am Coll Cardiol 1994,24(6):1460-7.
5. Ezekowitz MD et al. Amlodipine in chronic stable angina: results of a multicenter double-blind crossover trial. Am Heart J 1996,129(3):527-35.
6. van Kesteren HAM. A double-blind, comparative study of amlodipine vs diltiazem CR in the treatment of stable angina. Poster presentation, XVIIth Congress of the European Society of Cardiology, Amsterdam, August 23, 1995

REFERENCES: HYPERTENSION

1. NORVASC® Product Monograph, Pfizer Canada Inc., Dec. 19, 1997
2. Hernandez-Hernandez R et al. The effects of missing a dose of enalapril versus amlodipine on ambulatory blood pressure. Blood Pressure Monitoring 1996,1 121-6
3. Luscher TF and Cosentino F. The classification of calcium antagonists and their selection in the treatment of hypertension - a reappraisal. Drugs 1998,55(4):509-17.
4. Leenen FHH, Fourney A, Tanner J. Persistence of anti-hypertensive effect after interruption of therapy with long-acting (amlodipine) vs short-acting (diltiazem) calcium-antagonist. Clin and Investigative Medicine 1994,17(4) Suppl. B 70.
5. Hoegholm A et al. Comparative effects of amlodipine and felodipine ER on office and ambulatory blood pressure in patients with mild to moderate hypertension. J Human Hypertens 1995;9(Suppl 10):S25-S28
6. Ostergren J et al. Effect of amlodipine versus felodipine extended release on 24-hour ambulatory blood pressure in hypertension. Am J Hypertens 1998,11 690-6
7. Neaton JD et al. Treatment of mild hypertension study. JAMA 1993,270(6):713-24
8. Perna GP et al. Tolerability of amlodipine - A meta-analysis. Clin Drug Invest 1997,13(Suppl 1):163-68.

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FROM ONE DAY WELL INTO THE NEXT.

The Pyramids and Sphinx at Giza

℗NORVASC* (amlodipine besylate)

FOR HYPERTENSION

Long-acting BP control for mild-to-moderate hypertensives

- effectively controls BP at target levels for a full 24 hours and beyond[1,¶]
- intrinsically long half-life maintains plasma levels to reduce BP up to 24 hours after a missed dose[3,4†]
- shown to be more effective than felodipine at the same dose[5,¶]

Impressive tolerability after 4 years

- compared with antihypertensives from four different classes, more NORVASC* patients remained on therapy after 4 years[7‡]
- only 3% withdrawal rate among 12,831 patients in 16 clinical studies[8]

† NORVASC* should always be prescribed as once-daily therapy.
¶ NORVASC* 5-10 mg o.d. (n=103) versus felodipine ER 5-10 mg o.d. (n=103) after 8 weeks (p=0.036) 82% of NORVASC* patients reached target DBP of ≤90 mmHg versus 69% for felodipine.
‡ NORVASC* (n=114), 83% of NORVASC* patients remained on therapy after 48 months.

NORVASC* is indicated in the treatment of mild-to-moderate essential hypertension when diuretics or beta-blockers are unsuitable. The most common adverse reactions include edema (8.9%) and headache (8.3%).

Consult prescribing information for important safety information and drug interactions.

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PAAB

HERE TODAY. HERE TOMORROW.